JOURNAL OF THE
American Geriatrics Society
Official Journal of the American Geriatrics Society

Volume IX *June, 1961* Number 6

SYMPOSIUM ON CURRENT TOPICS IN CARDIOVASCULAR MEDICINE

INTRODUCTORY REMARKS—MORNING SESSION

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Washington, D. C.

The purpose of this symposium sponsored by the District of Columbia General Hospital is to present to practicing physicians, particularly in the District of Columbia and Metropolitan areas, some of the modern trends in the management of cardiac disorders. It is primarily a clinical symposium, but we have assembled speakers who have been working in both basic and clinical research. They will comment on present-day trends in heart research while orienting the listener primarily toward the practical aspects of their work.

Some of today's speakers will discuss work that has been performed at the District of Columbia General Hospital through the support of various grants. We are especially grateful to Hoffmann-La Roche company for their support of much of this work and for their grant-in-aid for this symposium.

In planning the symposium we have tried to cover a wide area in the field of cardiology, and believe that we have something of practical value to offer the physician who has to treat or deal with cardiac disorders. The entire program represents what we at the District of Columbia General Hospital consider our obligation to the community, namely, making available to practicing physicians in this area the new drugs with which we have had experience.

Following greetings from Dr. Daniel L. Finucane, Director of Health, the first section of this morning's program will be devoted to a discussion of certain elements in basic theory. Since this is not a research symposium there will be no attempt to present detailed research methods; attention will be directed only to those aspects that can serve as a theoretical foundation for the clinical program to follow. In the first section we shall hear from Dr. Alfred Pletscher of the Universities of Geneva, Zurich and Rome, and presently Director of Medical Research at Hoffmann-La Roche in Basle, Switzerland; Dr. Erminio Costa who was formerly with Dr. Harold E. Himwich at Galesburg Research Center, Illinois, and is currently Visiting Scientist in the Department of Chemical Pharmacology at the National Institutes of Health, Bethesda, Maryland; and Dr. Theodore Koppanyi, Professor and Chairman of the Department of Pharmacology at

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Georgetown University, Washington D. C. They will discuss various theories on endogenous metabolism, ganglionic transmission, and the possible mechanisms of action of monoamine oxidase inhibitors (MAO) with particular reference to angina pectoris.

This will be followed by the first panel discussion devoted to the role of MAO inhibitors in angina pectoris and hypertensive diseases. The discussion will be moderated by Dr. Henry I. Russek who is Consultant in Cardiovascular Disease, United States Public Health Service Hospital in Staten Island, New York and who has a wide background of experience in this field.

The second and final panel discussion for the morning session will be devoted to enzymes and the diagnosis of heart disease. The moderator for this group will be Dr. Howard Ticktin, Chief of the George Washington University Medical Service at the District of Columbia General Hospital, and Associate in Medicine at the George Washington Medical School. Dr. Ticktin has had considerable experience at Peter Bent Brigham Hospital, Boston, and is particularly conversant with the diagnostic use of enzymes in clinical medicine.

Chairman for the afternoon session will be Dr. John B. Johnson, Professor of Medicine and Chairman of the Department of Medicine at Howard University, Washington, D. C. Dr. Johnson has carried on considerable work of his own in cardiovascular diseases, particularly peripheral disorders.

WELCOMING ADDRESS

DANIEL L. FINUCANE, M.D.*

Washington, D. C.

It is my privilege to welcome you this morning to the Symposium on Current Topics in Cardiovascular Medicine. This symposium has been made possible by the joint sponsorship of the District of Columbia General Hospital, the District of Columbia Academy of General Practice, the District of Columbia Branch of the American Women's Medical Association, and the Maryland Academy of General Practice.

Much of the work under discussion today will be presented by the men who carried out the original research. The assemblage of such a faculty is a great credit to the individuals who worked so hard to establish and develop this symposium, and we owe them a debt of gratitude.

* Director of Public Health of the District of Columbia.

ON THE MECHANISM OF ACTION OF MONOAMINE OXIDASE INHIBITORS IN ANGINA PECTORIS*

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Monoamine oxidase (MAO) inhibitors of the hydrazine type have a variety of acute pharmacologic effects on the isolated heart as well as on the cardiovascular system in the intact animal. For example, they may cause changes in coronary flow, blood pressure, or the frequency, amplitude and force of contraction of the heart. These effects probably do not account for the beneficial action of MAO inhibitors in angina pectoris because the changes appear almost immediately after administration of the drug and because fairly large doses are required. In angina pectoris, the beneficial action is observed only after repeated medication during several days, and is obtained with much smaller dosages. Furthermore, comparison of the various MAO inhibitors shows that the clinical effect is probably not dependent upon the presence or upon the direction of the aforementioned pharmacologic alterations. There may be a similar beneficial effect on anginal pain regardless of whether a compound depresses or elevates blood pressure or whether its influence on coronary flow is pronounced or not (1).

In order to gain a better understanding of the mechanism of action of MAO inhibitors in angina pectoris, factors other than the acute pharmacologic effects have to be considered. The interpretation of such data is speculative, however, as long as the cause of anginal pain remains obscure. In this presentation, 4 typical actions of MAO inhibitors are discussed. These actions may account, at least in part, for the relief of pain in angina pectoris.

ACTIONS OF MONOAMINE OXIDASE INHIBITORS

1. Increase in 5-hydroxytryptamine content of blood

In both rabbits and humans, MAO inhibitors cause an increase of the 5-hydroxytryptamine (5HT) content of the blood platelets, even after repeated administration of doses in the therapeutic range (Fig. 1) (2, 3). The magnitude of the rise in 5HT seems to parallel the clinical potency of the various compounds. It has been found that 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine hydrochloride (isocarboxazid, Marplan) has the same effect on the 5HT content of blood platelets as does 1-pivaloyl-2-benzylhydrazine (Tersavid), but much lower doses are required. In angina pectoris, Marplan is generally effective in lower doses than Tersavid. Tersavid has less effect on the 5HT content of platelets as well as on anginal pain, in doses equimolecular to N_2-isopropyl isonicotinic

* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November 3, 1960.

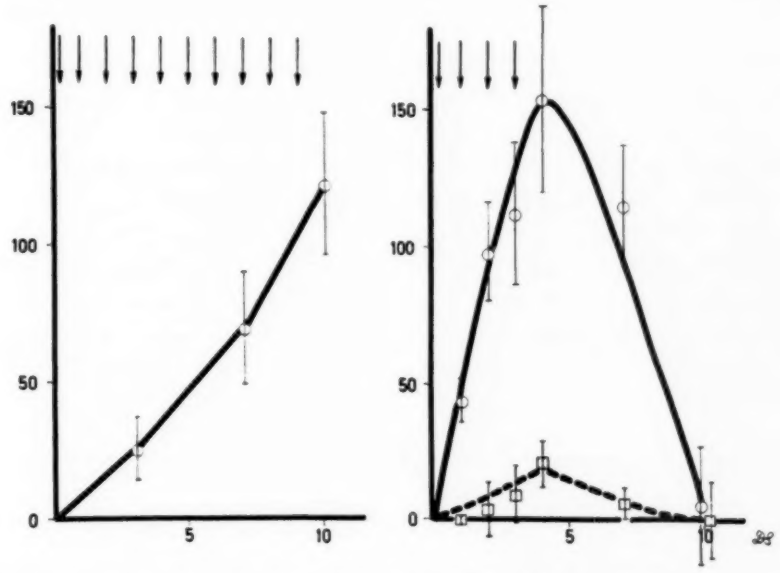

FIG. 1. Effects of 2 monoamine oxidase inhibitors (Marsilid and Rimifon) on the 5-hydroxytryptamine content of the blood and platelets. Abscissa: days of treatment. Ordinate: 5HT, in per cent. The points represent the average percentage 5-hydroxytryptamine increase in each group. Vertical lines represent the standard deviation.

Left-hand curve: isolated platelets in 5 human subjects. Each subject served as his own control. The 5-hydroxytryptamine content is referred to the platelet number. Arrows indicate oral administration of 5–8 mg. per Kg. of Marsilid.

Right-hand curves: whole blood of rabbits. Solid line represents i.v. administration of 30 mg. per Kg. of Marsilid (arrows) in 4 rabbits. Dotted line represents i.v. administration of 23 mg. per Kg. of Rimifon (dose equimolecular to that of Marsilid; arrows) in 4 rabbits.

acid hydrazide (iproniazid, Marsilid) (4). Nicotinic acid hydrazide (isoniazid, Rimifon) does not affect platelet 5HT content or anginal pain to any significant extent (2).

It has been debated whether the increase of 5HT in the platelets causes a decrease in anginal pain. In dogs, 5HT diminishes coronary vascular resistance and increases coronary flow, whereas the oxygen consumption of the left ventricle remains unchanged (5, 6). The increased platelet 5HT content might therefore act as a "benign coronary dilator" and account for the beneficial effect of MAO inhibitors in angina pectoris. According to recent investigations in humans, however, such a concept is probably no longer valid. It was shown that in patients with angina pectoris, in contrast to controls without angina, coronary flow could not be increased even with the classic coronary dilator, nitroglycerin; nevertheless, anginal pain was diminished (7). This indicates that the pain-decreasing effect of so-called coronary dilators is not necessarily due to an increase of coronary flow. It may therefore be concluded that the rise in 5HT content of the platelets influences anginal pain, if at all, by some mechanism other than coronary dilatation.

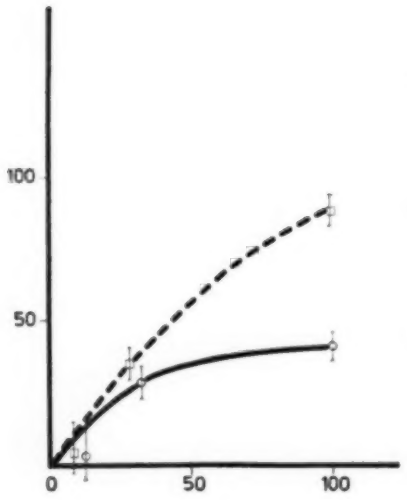

FIG. 2

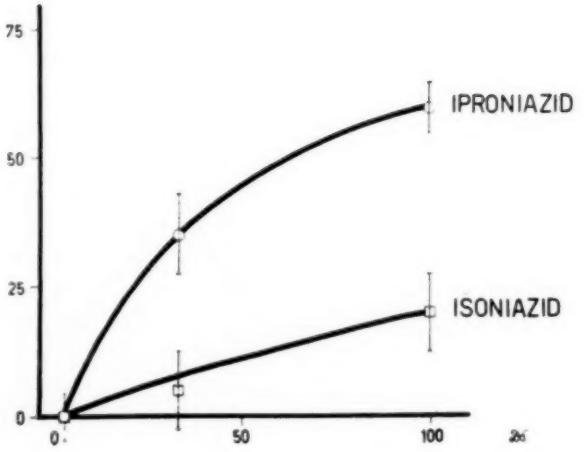

FIG. 3

FIG. 2. Effect of Marsilid on 5-hydroxytryptamine and catecholamine content of the brain of rats. Abscissa: dose in mg. per Kg. Ordinate: increase of 5-hydroxytryptamine and catecholamine content respectively as a percentage of the original value. Marsilid was given sixteen hours before killing the animals. Solid line: norepinenephrine. Broken line: 5-hydroxytryptamine. Each point represents the average of 4 to 20 measurements. Vertical lines represent the standard deviation.

FIG. 3. Percentage increase of endogenous norepinephrine in the heart of guinea pigs sixteen hours after i.p. injection of iproniazid (Marsilid) or isoniazid (Rimifon), (ordinate). Abscissa: doses of the drugs in mg. per Kg. Each point represents the average of 5 to 32 determinations with standard deviation.

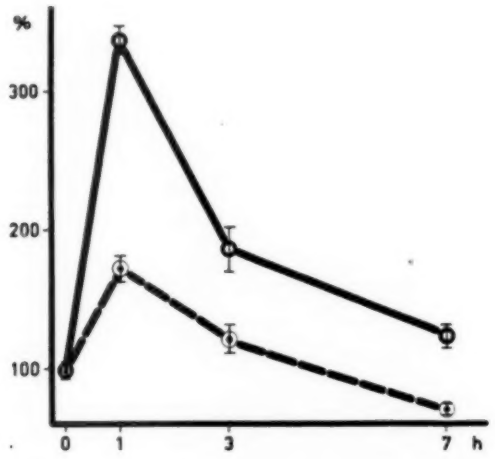

FIG. 4. Percentage increase of norepinephrine in the rat heart after i.p. injection of 5 mg. per Kg. of norepinephrine (ordinate). Abscissa: time in hours after norepinephrine injection. Broken line: controls without pretreatment. Solid line: intraperitoneal injection of 115 mg. per Kg. of Tersavid sixteen hours before administration of norepinephrine. Each point represents an average of 5 to 6 determinations with standard deviation. The difference between the Tersavid group and the control group was significant in all points ($P < 0.01$).

2. Blockade of neurohumoral transmission

MAO inhibitors of different chemical types inhibit nervous transmission in the isolated perfused superior cervical ganglion (8). In intact animals, however, MAO inhibitors of the hydrazine type show no evidence of a ganglion-blocking effect (9–12). Nevertheless, in humans, certain side-effects of hydrazine derivatives (*e.g.*, postural hypotension, sexual impotence or dryness of the mouth) possibly reflect a ganglionic blockade. Thus, it has been thought that MAO inhibitors might interfere with the transmission of anginal pain in the sympathetic pathways leading from the heart to the central nervous system (13). Blockage of such systems is conceivable since, in brain and sympathetic ganglia, MAO inhibitors alter the metabolism of catecholamines (12, 14) which may modify neurohumoral transmission (15) (Fig. 2). It remains to be proved whether such a mechanism is the principal pathway for the action of MAO inhibitors in angina pectoris.

3. Decrease of sensitivity to norepinephrine

The sensitivity of some parts of the vascular system to norepinephrine (NE) does not change or is even diminished after pretreatment with Marsilid or other MAO inhibitors. It has been shown that, in the dog, the action of NE and epinephrine on the contractile force of the heart and on blood pressure is not influenced by various MAO inhibitors of the hydrazine and harmane type (16, 17). Marsilid reduces the NE- and epinephrine-induced contractions of the small mesenteric vessels in rats and of the cutaneous vessels in rabbits (18). Furthermore, in our laboratories it was shown that NE-induced contraction of the isolated aorta diminished twenty hours after pretreatment of rabbits with Marsilid. Pretreatment with Rimifon, a weak MAO inhibitor, had no effect (19) (Table 1); this is in contrast with the action of DL-serine isopropylhydrazide, a strong MAO inhibitor (20). Marsilid *in vitro* also reduces the action of epinephrine on the isolated aorta (21).

TABLE 1

*Effects of Iproniazid (Marsilid) and Isoniazid (Rimifon) on the Norepinephrine-induced and 5HT-induced Contractions of the Isolated Rabbit Aorta**

		Pretreatment with	
		Iproniazid	Isoniazid
Norepinephrine	1γ	*37 ± 7*	93 ± 13
	5γ	*41 ± 4*	135 ± 25
5-Hydroxytryptamine	10γ	78 ± 22	90 ± 19

* Each value represents the maximal average contraction of 12 to 15 aortas, expressed as a percentage of the value for untreated controls. Experimental technique according to Furchgott and Bhadrakom (34). The animals were treated with 50 mg. per Kg. of Rimifon and equimolecular doses of Marsilid phosphate respectively, forty-four and twenty hours before removal of the aorta. Italic figures indicate that the decrease was significant ($P < 0.01$).

The mechanism of action of Marsilid is not clear. An interesting theory is based on the assumption that the NE reactivity of the cardiovascular system may depend upon the content of endogenous catecholamines. It has been shown that the response of blood vessels to NE increases if the amount of endogenous NE in the vessel wall is reduced by reserpine. Infusion of NE, which probably restores the endogenous NE, brings the NE reactivity of the vascular system back to normal (22). Therefore, the sensitivity of the vessels to NE seems to increase in association with a decrease in their content of endogenous NE, and *vice versa*.

Marsilid and other MAO inhibitors induce a rise in the endogenous NE content of the heart of certain animal species, *e.g.*, guinea pigs. This was first shown by the authors (12) using the method of Shore and Olin (23) (Fig. 3), and was reproduced recently in our laboratories with the somewhat more specific method of Bertler *et al.* (24). Furthermore, the increase in the heart caused by injection of NE was markedly enhanced by MAO inhibitors, *e.g.*, Marsilid or Tersavid (12) (Fig. 4).

Such a rise in catecholamines does not necessarily mean increased biologic activity or deleterious effects (25). The main part of the catecholamines may be stored in a biologically inactive state. Recent experiments confirm this point of view. Thus, the increase of NE in the heart due to administration of DOPA would have no effect on mechanical efficiency (26). An increased amount of stored endogenous NE might even have a beneficial effect in ischemic heart disease. As in the case of the aorta, the sensitivity of the heart to NE circulating in the blood or released from sympathetic nerve endings might conceivably be diminished. Such a mechanism would be consistent with the views of Raab that catecholamines are deleterious in angina pectoris (25). Further investigations are required to determine the validity of this hypothesis.

4. Effect on carbohydrate metabolism

Alterations in monoamine balance may affect carbohydrate metabolism. After the administration of several MAO inhibitors of different chemical classes (hydrazine derivatives, harmaline, phenylcyclopropylamine) to rats, a pronounced rise in the blood levels of lactic and pyruvic acid was observed. With all three classes of compounds, the duration of this effect paralleled MAO inhibition, *e.g.*, in the brain (Fig. 5). Furthermore, the rise in the blood lactic acid level caused by injection of epinephrine and NE was enhanced by pretreatment with Marsilid (Table 2). These findings indicate that the increase in the blood concentration of lactic and pyruvic acid after administration of MAO inhibitors may be due to changes in monoamine metabolism.

Inhibition of diamine oxidase (DAO) does not seem to be involved, since it has been observed that fairly typical DAO inhibitors (*e.g.*, aminoguanidine or semicarbazide) do not influence the content of lactic and pyruvic acid, whereas MAO inhibitors devoid of inhibitory effect on DAO (*e.g.*, phenylcyclopropylamine) cause an increase in these acids. A rise in the levels of lactic and pyruvic acids has also been found in the blood of patients with angina pectoris after successful treatment with MAO inhibitors (27).

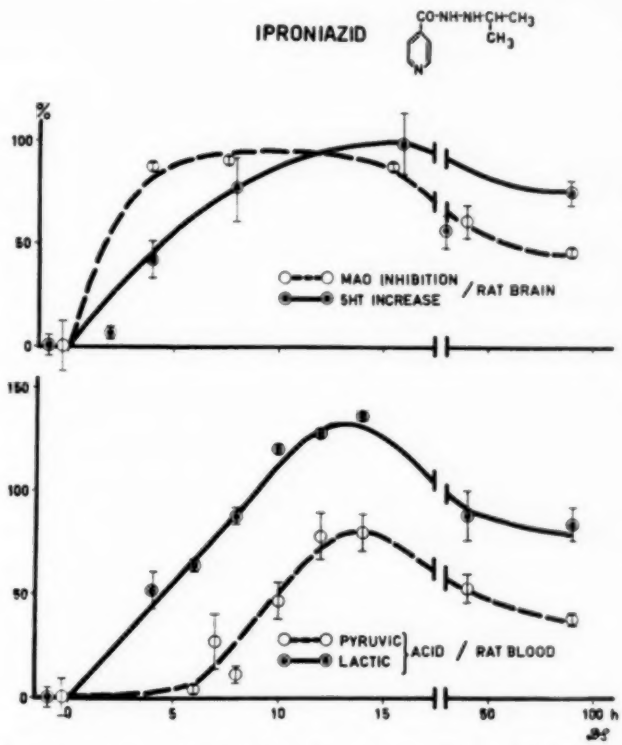

FIG. 5. Inhibition of monoamine oxidase and accumulation of 5-hydroxytryptamine in the brain compared with the changes in the pyruvic acid and lactic acid content of blood after administration of iproniazid (Marsilid). Measurement of MAO activity in the particulate fraction of the brain was carried out manometrically with tyramine as substrate (35); of 5HT in the whole brain, spectrophotofluorometrically (36); of lactic acid in blood serum (37, 38) and of pyruvic acid in total blood, by means of lactic dehydrogenase and DPN. Each point represents the average ± standard error in 8 rats (Wistar, female, 80–120 Gm., no food for sixteen hours) for MAO; in 4 to 11 animals for 5HT; in 4 to 12 rats for lactic acid; and in 5 to 12 rats for pyruvic acid. Doses (intraperitoneal) for the measurement of MAO were 20 mg. per Kg.; for the measurement of 5HT, lactic and pyruvic acid they were 100 mg. per Kg.

The effect of increased blood levels of lactic and pyruvic acid on angina pectoris is not clear. Lactic acid seems to be an important source of energy for the heart (26). A continuous rise of this acid in the blood might therefore improve the metabolic conditions of the hypoxic myocardium and exert a beneficial effect on anginal pain.

Evidence that MAO inhibitors improve pathologic alterations due to hypoxic conditions has been obtained in previous studies. Thus, the effect of hypoxia in various experimental situations (myocardial infarction, lack of oxygen in the perfusion fluid for isolated rabbit heart, skeletal muscle with ligated arteries, isolated skeletal muscle, or animals in a nitrogen atmosphere) was diminished by the use of Marsilid (28–30). Marsilid prevented the onset of ventricular fibrillation and death in dogs with coronary occlusion (31) and prevented myocardial necrosis due to isopropyl-arterenol injections (32, 33).

The foregoing considerations show that the mechanism of action of MAO in-

TABLE 2

*Effect of Catecholamines on Serum Lactic Acid Level in Rats Pretreated with Marsilid**

Injected Monoamine	Serum Lactic Acid (mg. 100 ml.)		P
	without Marsilid	with Marsilid	
—	22 ± 1	30 ± 3	<0.01
Epinephrine	76 ± 10	99 ± 10	<0.05
Norepinephrine	40 ± 4	80 ± 4	<0.01

* L(+)-lactic acid in the serum thirty minutes after intraperitoneal injection of 0.5 mg./Kg. of epinephrine hydrochloride or 2.5 mg./Kg. of norepinephrine bitartrate. Pretreatment with 100 mg./Kg. of Marsilid intraperitoneally sixteen hours before injection of the amines.

hibitors in angina pectoris is not yet clear. The current findings, however, support the view that alterations of monoamine metabolism at least partly account for the clinical effect. The action of MAO inhibitors on carbohydrate metabolism, in particular, constitutes an interesting new fact which may possibly lead to a better understanding of the mechanisms that cause and counteract anginal pain.

SUMMARY

The following possible mechanisms for the action of monoamine oxidase (MAO) inhibitors in angina pectoris are discussed: 1) an increase in the 5-hydroxytryptamine content of the platelets, resulting in coronary dilatation; 2) a blockade of pain transmission due to alterations of monoamine metabolism in the central nervous system and sympathetic ganglia; 3) a decrease in the sensitivity of the heart to norepinephrine (NE) because of enhanced storing of endogenous NE; and 4) an increase in the levels of lactic and pyruvic acid in the blood, leading to improved metabolic conditions in the heart.

Of these four mechanisms, the first seems unlikely, and the other three need further elucidation.

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A ROLE FOR NOREPINEPHRINE IN GANGLIONIC TRANSMISSION*

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Hypertension, regardless of its etiology, is usually manifested by increased tone of the sympathetic nervous system, a condition which may be due either to an abnormally large amount of norepinephrine at the nerve endings or to hyperresponsiveness of arterial smooth muscle to the action of this catecholamine. Most hypotensive drugs lower sympathetic tone in one of several ways: 1) by inhibiting the action of norepinephrine released at neuro-effector junctions (adrenergic blocking agents); 2) making norepinephrine unavailable to neuro-effector junctions by depletion of the catecholamine stores (reserpine, syrosingopine, guanethidine, α-methyl Dopa) or by prevention of the physiologic release of catecholamines (bretylium); 3) reducing the flow of traffic in sympathetic nerves by suppression of the central sympathetic centers (central adrenergic blocking agents); and 4) reducing sympathetic traffic by blockade of the peripheral sympathetic ganglia.

This paper is a brief report of studies on sympathetic ganglion cells, which indicate that norepinephrine modulates sympathetic synaptic transmission. It is hoped that these results may contribute toward further insight into the mechanisms that control blood pressure and provide a fresh clue to the cause of hypertension.

Acetylcholine liberated at nerve endings has long been known to cause the release of catecholamines from the adrenal medulla. Recently Burn and Rand (1) suggested cogent arguments in favor of the concept that postganglionic sympathetic nerves are in reality cholinergic, and that acetylcholine released at these nerve endings causes the release of norepinephrine. According to this view, norepinephrine is not a chemical transmitter of impulses across neuro-effector junctions but a local hormone which causes muscle fibers to contract.

Since peripheral sympathetic ganglia contain fairly large amounts of norepinephrine (2), we raised the question whether here, too, the amine might not be released by acetylcholine and perhaps have an important role in the regulation of ganglionic transmission. Marrazzi and associates (3) demonstrated that the injection of epinephrine and norepinephrine causes inhibition of synaptic transmission in sympathetic ganglia. These results suggest that the norepinephrine localized in ganglia may have the function of modifying synaptic transmission. However, responses to the injection of a biologically active substance may be nonspecific pharmacologic effects which do not define its normal role in the body. For example, the injection of histamine and even serotonin, a substance not even present in sympathetic ganglia, also elicits a change in ganglionic transmission (4, 5). We decided that determining the effect of depleting ganglionic

* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November 3, 1960.

norepinephrine would be a more direct approach to elucidation of the role of the amine in ganglionic transmission.

EXPERIMENTAL

Our observations were made on cats and rabbits anesthetized with chloralose. Changes in synaptic transmission were determined by applying a graded electrical stimulus to a group of synapses (in this case the superior cervical sympathetic ganglion), and recording the electrical activity postganglionically before and after the intravenous injection of reserpine in various doses.

Reserpine in doses up to 0.2 mg. per Kg. had no effect on ganglionic transmission; a definite increase was produced with a dose of 0.6 mg. per Kg., and maximal enhancement occurred with 1.25 mg. per Kg. In control animals, not given reserpine, the evoked potential remained relatively constant over a period of twenty hours.

Postganglionic responses evoked by submaximal and supramaximal stimuli were measured at various times after the administration of reserpine (2.5 mg. per Kg). After a latent period of about four hours, the evoked potential was definitely higher than the control value; the increase continued, was maximal in about seven hours, and persisted throughout the twelve hours of the experiments. An increased response was obtained after submaximal or supramaximal stimuli. In some experiments, stimuli which produced no effect in the control period now evoked a potential equal to the greatest response produced by supramaximal stimuli. These findings indicate that reserpine may upset the mechanism which normally controls the number of cells firing in response to preganglionic electrical stimuli. In absence of this control only a small stimulus is required to activate all the cells.

The relationship between the content of ganglionic norepinephrine and ganglionic transmission is shown by the results of fluorometric assay of the superior sympathetic ganglion. For this purpose a recently published procedure which measures as little as 0.040 μg. of catecholamine was used (6). The assay showed that ganglionic norepinephrine was lowered by more than 90 per cent when maximal potentiation of synaptic transmission was obtained.

Experiments in cats with adrenergic blocking agents and bretylium provided additional evidence of a role for norepinephrine in ganglionic transmission. Within twenty minutes after the injection of 1 mg. of ergotamine per Kg. the evoked potential was markedly facilitated for a period of at least one hour. Similar effects were produced with dibenamine. Incidentally, this is the first demonstration that adrenergic blocking agents exert an action at sympathetic ganglia.

Bretylium, a hypotensive drug that prevents the physiologic release of norepinephrine from nerve endings (7), also facilitated ganglionic transmission. The first effect observed after injection of 20 mg. per Kg. of the drug was a blockade of ganglionic transmission which lasted for about thirty minutes, following which the evoked potential was greatly enhanced for a period of about twelve hours.

Since transmission was found to be enhanced in ganglia devoid of norepinephrine, we wished to determine whether transmission would be inhibited in ganglia containing excess amine in the free form. A high level of free norepinephrine in ganglia was produced by pretreating cats with MO 911, a potent monoamine oxidase inhibitor, and then releasing the amine with reserpine. As a result of the blocking of monoamine oxidase, the disappearance of norepinephrine released in ganglia by reserpine was slow, occurring over a period of several hours compared with the relatively rapid disappearance from ganglia of animals given reserpine alone. Within fifteen minutes after administration of the alkaloid, the potential evoked by submaximal stimuli was almost completely blocked, and even the potential evoked by supramaximal stimuli was markedly reduced. In a few hours when the free norepinephrine had finally diffused away, facilitation of the evoked potential was again observed.

COMMENT

In this communication, we have presented evidence that transmission across sympathetic ganglia is regulated by norepinephrine as well as by acetylcholine; in some way, norepinephrine in ganglia is released by acetylcholine and then counteracts the synaptic response to the quaternary transmitter. According to this view norepinephrine modulates synaptic transmission in some unknown fashion, possibly by a feedback mechanism. This reciprocal relationship between acetylcholine and norepinephrine at the sympathetic ganglia may be important in the regulation of blood pressure homeostasis, by holding within bounds the results of large changes in central sympathetic acitivity. A pronounced increase in sympathetic output could have catastrophic cardiovascular effects by causing all the postganglionic sympathetic cells to fire at one time; this might be prevented by the antagonistic influence of norepinephrine. In contrast, the effect of a great reduction in sympathetic outflow would be lessened by the diminished release of antagonistic norepinephrine at the ganglia. In this way norepinephrine in ganglia could diminish the peripheral effects of wide swings in central sympathetic output. Such a feedback mechanism might also explain why a number of potent, centrally-acting, sympathomimetic drugs elicit relatively small rises in blood pressure. Many of these substances, such as amphetamine, also depress synaptic transmission, perhaps by mimicking the action of norepinephrine.

It is worth while to consider the possibility that some forms of hypertension are due to a defect in the mechanism by which norepinephrine modulates ganglionic transmission, and that hypotensive drugs may be discovered which selectively interact with the norepinephrine-acetylcholine mechanism at the ganglia. In fact, the question arises whether the hypotensive action of monoamine oxidase inhibitors might be explained by an elevated level of norepinephrine in ganglia. Animal experiments show that high doses of monoamine oxidase inhibitors reduced the amplitude of the evoked potential. However, this reduction is of short duration and is unrelated either to the duration of monoamine oxidase inhibition or to the rise in the level of ganglionic norepinephrine. Further

studies are required before the possibility can be excluded that monoamine oxidase inhibitors may modify ganglionic transmission.

CONCLUSIONS

Transmission across sympathetic ganglia may be regulated by norepinephrine as well as by acetylcholine, acting in a feedback mechanism. This reciprocal relationship may be important in the regulation of blood pressure homeostasis.

The possibility that monoamine oxidase inhibitors may modify ganglionic transmission needs further study.

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DISCUSSION OF THE PAPERS BY DOCTORS PLETSCHER, COSTA AND BRODIE*

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The discovery by Hare (1) in 1928 of a liver enzyme catalyzing the oxidative deamination of tyramine was followed by the identification of this enzyme as monaminoxidase (MAO). It occurs abundantly in the liver mitochondria and microsomes. Distribution of this enzyme is fairly ubiquitous—its presence in autonomic ganglia can be demonstrated, as Drs. Costa and Brodie emphasized in their presentation. MAO inhibitors may produce an accumulation of monoamines in the tissues—most importantly, in target organs. Their effect is usually preceded by a fairly long latent period, with the notable exception of harmaline.

Dr. Pletscher's paper was mainly concerned with the mechanism of action by which these agents diminish or abolish the pain that is characteristic of angina pectoris. Since MAO inhibitors increase the coronary flow, one may be tempted to attribute their anti-anginal effect to this phenomenon. However, it cannot be the most important reason because even nitroglycerine, although it abolishes anginal attacks in patients with angina pectoris, usually does not increase coronary flow. MAO inhibitors depress cardiac contractility, elevate blood glucose, lactic acid and pyruvic acid levels, have a psycho-energizing effect, and possess at least fleeting ganglionic blocking properties. Therefore, it is more probable that one of these actions, or a combination of them, accounts for the clinical results obtained in angina with MAO inhibitors. Should the mechanism of action be based on the depression of cardiac contractility, then drugs which cause a negative inotropic effect should usually possess anti-anginal properties. Moreover, in patients in whom anginal pain is accompanied by congestive failure (hypodynamic heart), the chest pain should either be diminished or fully abolished. The hypothesis that the elevation of the blood levels of glucose, lactic acid and pyruvic acid accounts for the anti-anginal effect of MAO inhibitors could be tested with a number of drugs which have no action on MAO. If, on the other hand, ganglionic transmission is involved in the alleviation of anginal pain, the focus of attention should be directed to sensory and not to motor ganglia. It is of prime importance that afferent synapses (such as nodose ganglia) be investigated. This can be accomplished by fairly simple experimental techniques.

At the present stage of our knowledge, central effects (specific stimulation, accompanied by inattention to pain) cannot be ruled out (2). Therefore, other psycho-energizers and related compounds should be tested for their anti-anginal effects. If only MAO inhibition is involved in the successful management of angina pectoris by specific enzyme inhibitors, then harmaline should prove to be a

* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November 3, 1960.

quick-acting drug. The actions of some other MAO inhibitors, exemplified by the hydrazines, are slow in onset. In some preliminary investigations, this difference has already been corroborated. However, a large-scale clinical study with harmaline and related compounds is made rather difficult because of their toxicity (3). The hydrazines are moderately analgesic, as shown by the phenylquinone-induced writhing syndrome and the findings with the Eddy hot-plate method (4). Although there is evidence that this analgesic action is independent of catecholamine or 5-hydroxytryptamine accumulation, nevertheless MAO inhibitors appear to potentiate the analgesic effects of 5-hydroxytryptophane and dihydroxyphenylalanine (also norepinephrine?).

There is no question that endogenous norepinephrine (NE) is present in the autonomic ganglia, nor can it be doubted that norepinephrine and other catecholamines—indeed, many sympathomimetic amines, of diverse structure—may influence synaptic transmission. However, the role of norepinephrine in the ganglia is not fully clarified; some workers have reported that small doses of the amines depress synaptic transmission (5), whereas other workers have reported that small doses facilitate transmission and only large doses depress it (6). The studies by Drs. Costa and Brodie indicate that the NE present in ganglia actually depresses synaptic transmission. I commend their ingenious methods of lowering and raising the NE content of sympathetic ganglia, and the close agreement between their biochemical and neurophysiologic findings.

Following the release of NE by reserpine in the presence of MAO inhibitors, free NE accumulates in the ganglia and causes a block. Reserpine alone in the absence of MAO inhibitors also releases NE from its ganglionic depots, but the catecholamine is metabolized; thus mere reserpinization facilitates ganglionic transmission. It may be assumed that the bound and the free NE exist in a state of dynamic equilibrium in the sympathetic ganglia. It would seem that during cholinergic ganglionic stimulation and/or transmission, signals are sent out to the chromaffin cells to release more or less NE, as required. According to this concept, NE modulates this action of acetylcholine, possibly by a feedback mechanism.

A new concept presented by Drs. Costa and Brodie is that peripherally acting adrenergic blocking agents, such as ergotamine or dibenamine, also block at the ganglionic level; this was hitherto unsuspected. Their paper indicates very strongly that the high concentrations of NE found in the ganglia are bound, and thus are physiologically inert because reserpine is needed to mobilize them from their depot sites. It would be interesting to learn whether administration of MAO inhibitors alone, without reserpine, might also bring about inhibition of synaptic transmission. Although the results of this preliminary study by Drs. Costa and Brodie indicate that the mere blocking of monaminoxidase does not (or only fleetingly) inhibit synaptic transmission, the *hypotension* produced by MAO inhibitors shows that additional experimentation in this field is warranted.

A further question may be posed: Is it possible that inhibitory concentrations of NE in the ganglia also produce a blockade to injected acetylcholine? Perhaps,

with the use of an experimental set-up like that devised by Drs. Costa and Brodie, one could confirm Bülbring's observation that the larger doses of catecholamines, after producing a transitory augmentation, depress the effects of exogenous acetylcholine.

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PANEL DISCUSSION ON THE CLINICAL APPLICATION OF AMINE OXIDASE INHIBITORS IN ANGINA PECTORIS AND HYPERTENSION

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We are fortunate to have as our panelists four distinguished physicians who have extensive experience in the cardiovascular field. The first two speakers, Dr. Robert Oblath, Associate Clinical Professor of Medicine, University of Southern California Medical School at Los Angeles, and Dr. Andrew Prandoni, Associate Professor of Clinical Medicine, George Washington Medical School, Washington, D. C., will discuss the use of amine oxidase inhibitors in angina pectoris. The last two speakers, Dr. Frank Finnerty, Assistant Professor of Medicine and Pharmacology at Georgetown Medical School, Washington, D. C., and Dr. Marvin Moser, Chief of Hypertension Clinic at the Montefiore Hospital in New York City will comment on the hypotensive action of the amine oxidase inhibitors.

Interest in the amine oxidase inhibitors for the treatment of angina pectoris has stemmed from the serendipitous discovery by Dr. Teodoro Cesarman in 1957 that iproniazid[1] remarkably reduced the frequency and severity of anginal attacks in cardiac patients under treatment for depression. Since that time, numerous studies have confirmed this action of iproniazid and have demonstrated that similar effects may be obtained with a less toxic and better tolerated analog of the parent drug.

In the course of treatment with amine oxidase inhibitors, both for depression and for angina pectoris, hypotensive effects have been observed in some instances. Investigators have sought to determine whether this hypotensive action might be utilized in the treatment of hypertension, but as yet no definite statement can be made either for or against such therapy.

The mode of action of amine oxidase inhibitors in the production of anti-anginal effects is not known, but we can venture an opinion as to what actions are *not* operative. The improvement in exercise tolerance and capacity for work in patients with angina pectoris who are receiving amine oxidase inhibitors is not due to improvement in the coronary circulation, enhancement of myocardial metabolism, or increased oxygen uptake by the myocardium. We base this conclusion on the fact that in patients who are relatively free from angina while taking these drugs there is no significant change in the electrocardiographic response to measured exercise during therapy.

Thus, it would appear that the benefit from amine oxidase inhibitors is symptomatic, and that we are actually treating the neuralgic manifestations of myocardial ischemia. It would also appear that the mode of action may be a blockade of painful stimuli from the heart to the conscious centers of the brain.

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[1] Marsilid, Hoffmann-La Roche Inc., Nutley, New Jersey.

Potentiation of adjunctive medications such as nitroglycerin, has been observed in patients taking amine oxidase inhibitors; in fact, with the more potent inhibitors, there may be hyperresponsiveness to nitroglycerin and a precipitous drop in blood pressure. Consequently, many patients have been advised to use smaller doses of nitroglycerin while taking the more potent amine oxidase inhibitors. However, this hypotensive reaction to the nitrates has not been observed during treatment with drugs like Tersavid.

It has also been reported that silent infarction may occur while patients are being treated with these agents. Our group has treated well over 100 patients with one or another amine oxidase inhibitor and we have never seen a case of silent myocardial infarction.

EXPERIENCES IN THE TREATMENT OF ANGINA PECTORIS WITH MONOAMINE OXIDASE INHIBITORS*

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The purpose of this paper is to report our experiences with the monoamine oxidase (MAO) inhibitors in the treatment of angina pectoris. We first used iproniazid after Cesarman's initial report in 1957 (1), and have found this drug and its analogues to be valuable agents in the treatment of this condition. At the present time they are our choice of "prolonged-action type" drugs for the long-term treatment of severe angi a. Because of its reported toxicity, we have not used iproniazid regularly since February 1959.

In this communication we shall therefore consider primarily isocarboxazid (Marplan), pivalylbenzhydrazine (Tersavid), and a new substance, 1-(p-dimethylaminobenzyl)-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine, or Ro 5-1025. Isocarboxazid was used exclusively until June 1959, when pivalylbenzhydrazine was made available; since then, only this agent has been used, except in a few patients who either could not tolerate it or did not improve as much as with isocarboxazid. One of us (RWO) has recently used Ro 5-1025 in a few cases of angina.

CLINICAL MATERIAL AND METHODS

In the majority of the patients studied, angina pectoris was secondary to coronary arteriosclerosis; a smaller group suffered from angina secondary to aortic valvular disease. The ages and distribution of the patients were those usually observed in association with this condition.

Thirty-five patients were treated with isocarboxazid, 60 with pivalylbenzhydrazine, and 7 with Ro 5-1025. The duration of treatment (including that for several subjects who were given various preparations sequentially) was from one to thirty-two months.

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* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November 3, 1960.

In evaluating the results we considered the following factors: 1) the severity of the pain, 2) the average weekly number of anginal attacks, and 3) the number of nitroglycerin tablets used daily. Severity of pain was graded from 1 to 4, *i.e.*, from barely noticeable angina to almost complete disability. The patient's capacity for effort was also assessed. For example, several patients did not decrease their nitroglycerin intake with treatment, but doubled or otherwise increased the amount of effort exerted before pain was induced. The over-all response was judged as follows: 75–100 per cent improvement in the factors noted—"marked benefit"; 50–75 per cent—"good"; 25–50 per cent—"fair"; and less than 25 per cent, "no response."

Each of these agents was administered by one of two methods: 1) large doses initially, tapering off to a maintenance level, or 2) small doses initially, building up to maximal action. The former method achieves results more rapidly; the latter allows more precise individualization of the dosage. Either method is acceptable and useful, and selection should be made on the basis of greater benefit to the individual patient.

In place of a control series, each patient served as his own control. Since each subject had been observed and treated for a long period, his responses to previous new medications were well known. The peculiar characteristic of MAO inhibition—a delay of several days before the therapeutic effect becomes evident—helped in the evaluation. Any action in patients susceptible to administration of placebo would be evident before the medication could possibly have achieved a pharmacologic effect, *i.e.*, after only one dose. A group of patients was treated with each of the agents, sometimes with a change of dosage during the study period. In every case, either exacerbation or relief of pain usually occurred two to seven days after each change of drug or adjustment of the dosage. The time period in each instance so closely paralleled the expected time of action of MAO inhibitors as to lend strong support to the validity of using these patients as their own controls. The effect on anginal pain is illustrated in Figure 1.

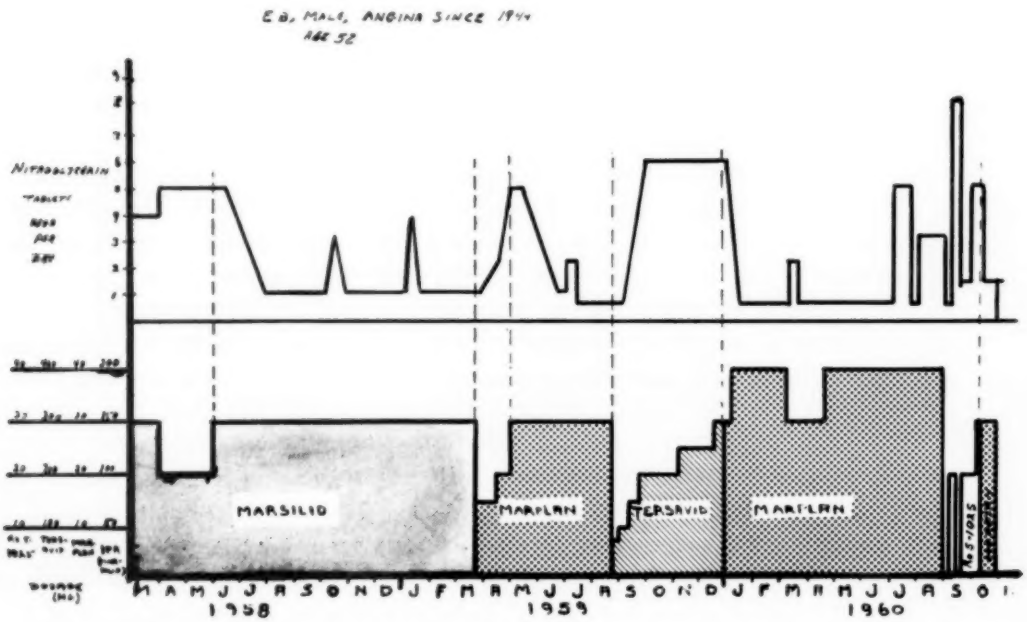

FIG. 1. The pharmacologic effect of MAO inhibitors. Note the waxing and waning of angina as either the dose or the type of MAO medication was changed. The vertical broken lines indicate the delay in onset or subsidence of the effect in relation to the change from one preparation to another, or to the change in dosage.

RESULTS

Isocarboxazid (Marplan)

In June 1959 we reported our experiences with isocarboxazid (2). The results were good in 21 patients, including 3 who could not tolerate or did not benefit from other preparations. The initial dosage was usually 10–15 mg. per day; once weekly this was increased by 5–10 mg. daily to a maximum of 30 mg. daily. One patient was maintained with, and tolerated, 40 mg. daily for several months. In 2 other patients in whom it was necessary to give 40 mg. per day, nervousness, tremors, and clonic movements developed; these symptoms subsided when the dosage was reduced to 30 mg. per day. After maximal benefit had been achieved, attempts were made to reduce the dosage to a maintenance level; the majority of patients were treated with 20–30 mg. daily; the maximal dose was 30 mg., the minimum 10 mg.

Marked benefit was observed in 21 (60 per cent) of the 35 subjects, good results in 5 (14 per cent), questionable results or no relief in 7 (20 per cent), and enhancement of the angina in 2 (6 per cent), as indicated in Figure 2.

In addition to nervousness, tremors and clonic movements in 2 cases, minor side-effects such as looseness of bowels, metallic taste, and dryness of the mouth were noted occasionally. These symptoms did not interfere with treatment.

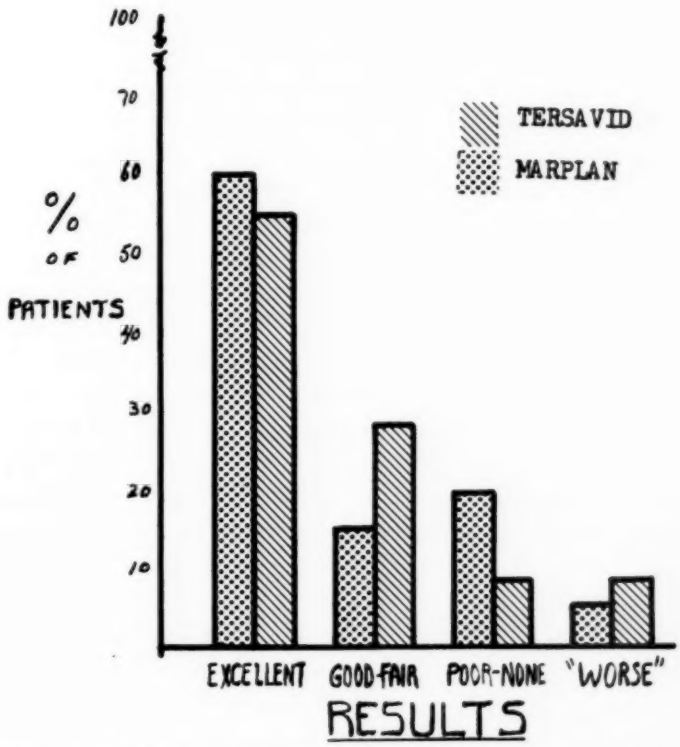

FIG. 2. Comparison of the effects of pivalylbenzyhydrazine (Tersavid) and isocarboxazid (Marplan) in the treatment of angina pectoris. (See text for details.)

In 1 patient nausea and emesis developed with larger doses, but disappeared when the dose was reduced. In 1 patient severe orthostatic hypotension developed during treatment with 15 mg. daily; after discontinuation of isocarboxazid, recovery took place within five days. No abnormalities were revealed by physical examination, urinalysis and blood counts. None of these patients showed evidence of hepatic damage.

Pivalylbenzhydrazine (Tersavid)

Sixty patients have been treated with this agent since June 1959—first with pivalylbenzhydrazine base, but since July 1960 with pivalylbenzhydrazine hydrochloride. No difference was noted between the effects of these two forms. Initially, relatively small dosages (50–75 mg. daily) were used, but more recently the best results were obtained with 100 mg. per day or more, later adjusting the dose as necessary. There were wide individual variations, however; in some cases it was necessary to prescribe as much as 300 mg. daily. The smallest effective dosage was 50 mg. per day in several patients. In some instances, when results were poor with low doses, striking benefit was obtained with large doses. The usual range of maintenance dosage was 75 mg. to 200 mg. per day.

Results in this series were judged as in the isocarboxazid series. Of the 60 patients, 33 (55 per cent) were markedly benefited; 17 (28.3 per cent) obtained moderate relief; 5 (8.3 per cent) were not helped; and 5 (8.3 per cent) became either depressed or jittery and nervous (Fig. 2). Treatment was discontinued in this last group, and the symptoms subsided.

The patient who previously had severe orthostatic hypotension while taking isocarboxazid was maintained with 50 mg. of pivalylbenzhydrazine daily for at least a year, almost completely free of angina. The small daily requirement of pivalylbenzhydrazine paralleled the small daily requirement of isocarboxazid.

No serious side-effects were noted during the use of pivalylbenzhydrazine. No significant changes were revealed by physical examination, urinalysis and blood counts. Hepatic function tests, including determination of serum pyruvic and glutamic transaminase activity, direct, indirect and total bilirubin, alkaline phosphatase, thymol turbidity aad cephalin flocculation, yielded normal values throughout treatment in the cases in which they were performed.

It is noteworthy that no patient experienced orthostatic hypotension while being treated with pivalylbenzhydrazine. Urticaria and pruritus shortly developed in 1 patient after starting treatment; recovery was spontaneous and the patient continued to take the medication without further difficulty.

Ro 5-1025

Experience with Ro 5-1025 has been so limited that no conclusions can be drawn. This drug was administered to 7 patients for periods of one month or more. One of these patients could not tolerate this (or any other) MAO inhibitor, even in very small doses, without extreme agitation and sleeplessness. One patient stopped all medications when coronary insufficiency developed after she had played in several golf tournaments. Good results were obtained in 4 patients,

usually with 20 mg. daily; however, in 1 of these the benefits were fleeting and isocarboxazid was resumed, with relief of angina. In another of the 4, mild asymptomatic orthostatic hypotension developed; pivalylbenzhydrazine was substituted without benefit and the patient became depressed; Ro 5-1025 was started again, this time with benefit. In the remaining 2 patients, progress has been satisfactory.

Several patients have died since the study began, but in no case could the death be related to the use of an MAO inhibitor or to a supposed silent myocardial infarction. One patient, examined at autopsy, showed no histologic or gross evidence of any changes which could be related to the use of MAO inhibitors.

COMMENT

MAO inhibitors are extremely valuable in the long-term treatment of angina pectoris. They have a striking effect in reducing the number of attacks of angina as well as the number of nitroglycerin tablets required in most cases. Moreover, this effect is usually not transient, but persistent.

The availability of several such preparations is advantageous, since treatment can be more easily tailored to fit the individual patient if the physician has a choice of agents. Thus, the depressed patient can be given isocarboxazid, or the over-active patient can be treated with pivalylbenzhydrazine. Continued benefit can be obtained in cases complicated by orthostatic hypotension by changing to another preparation which does not produce such side-effects.

SUMMARY

In this study of the effect of monoamine oxidase inhibitors in angina pectoris, 35 patients were treated with isocarboxazid, 60 with pivalylbenzhydrazine, and 7 with Ro 5-1025. In the first two series, striking and prolonged benefit was observed in 54 patients, good results in 22, questionable or no response in 12, and either an augmentation of angina or the development of side-effects in 7. No toxicity was noted. The side-effects were minor and few, except for severe orthostatic hypotension in 1 patient during isocarboxazid therapy; in only 1 case was it necessary to terminate treatment. In the Ro 5-1025 series the number of patients was so small and the duration of treatment so short that no valid conclusions could be drawn regarding either benefits or side-effects.

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DOUBLE-BLIND EVALUATION OF AN IPRONIAZID ANALOG (RO 4-1634) IN THE TREATMENT OF ANGINA PECTORIS* †

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Numerous clinical reports have indicated that certain monoamine oxidase inhibitors may have value in the treatment of angina pectoris. Unfortunately the initial favorable results were soon followed by reports of objectionable side-effects and occasional severe toxic reactions (primarily hepatic). Consequently, other compounds possessing similar enzyme-inhibiting properties are being developed in an attempt to achieve a safe and acceptable drug that will retain the beneficial action of the earlier compounds, of which iproniazid may be considered the prototype. One such substance is Ro 4-1634 (1-benzyl-2-trimethyl-acetyl-hydrazine), an iproniazid analog. It has one and a half times the monoamine oxidase-inhibiting action of iproniazid, but is much better tolerated by animals (1). No serious side-effects have been observed in patients receiving this medication in dosages up to 150 mg. daily. Accordingly, a study was undertaken to evaluate its effects in a group of patients with typical angina pectoris. This report summarizes our findings.

MATERIALS AND METHODS

Twenty-seven subjects with typical angina pectoris were selected from the patients in active attendance at the Cardiac Clinic of the George Washington University Hospital. The sole basis for selection was unequivocal evidence of coronary heart disease. The initial examination and monthly evaluations were conducted by one of us (J. B. C.). Seven subjects were subsequently excluded from the study because they failed to keep clinic appointments or moved to another locality. Of the remaining 20 patients, 14 were males and 6 were females; their ages ranged from 42 to 78 years. They were evenly divided between Negroes and whites. The electrocardiogram was abnormal in 16, and 6 had had one or more myocardial infarctions. There was roentgenographic evidence of cardiomegaly in 12 patients. Either hypertension or congestive heart failure was being treated prior to the present study, and the therapy of these conditions remained unchanged throughout.

The severity of anginal symptomatology was graded according to the classification of Greiner and associates (2). Three cases were classified as 1+, 9 cases as 2+, and 8 cases as 3+.

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* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November 3, 1960.

† This study was supported by a grant from Hoffmann-La Roche Inc., Nutley, N. J.

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This study was conducted in double-blind fashion; the 2 compounds compared were Ro 4-1634 (Tersavid)[1] and a lactose placebo. These substances were identified by code numbers assigned from a table of random numbers (3). The dosage of Ro 4-1634 was 25 mg. (one tablet) three times a day, and a sufficient quantity was dispensed to last for four weeks. This time period was chosen because of the prolonged action of the drug (1). Each patient was treated for 4 such periods (2 drug and 2 placebo); these trials were conducted in random sequence. Upon conclusion of the double-blind study, Ro 4-1634 was continued in a dosage of 100 to 150 mg. daily for further evaluation. The subjects were instructed to take nitroglycerin tablets according to their usual habit (as needed). The average number of tablets required daily was used as a standard for measuring the effectiveness of Ro 4-1634 in each case.

The data relating to the subjective effect of either the placebo or Ro 4-1634 were obtained from a "daily report card" as used by Greiner and associates (2). A second card was given to each patient for the purpose of recording the number of nitroglycerine tablets taken daily. At each clinic visit an interval history was recorded, with particular reference to side-effects of therapy; a cardiovascular examination was also made. Blood pressure readings were obtained with the patient sitting and then standing, because previous reports had indicated that postural hypotension may be one consequence of treatment with monoamine oxidase-inhibiting compounds (4). During the investigation the following laboratory studies were made: complete blood count, urinalysis, electrocardiogram, roentgen film of the heart, determination of the blood urea nitrogen level, and periodic determinations of the serum glutamic oxaloacetic transaminase level.

In the final tabulation of the results, the first ten days of each treatment period were excluded in order to minimize the effects of overlapping from the preceding month's therapy. For statistical evaluation, a nonparametric technique was employed, namely, the Willcoxon matched-pairs signed-ranks test (5). A one-tail test procedure was used because we were primarily interested in determining whether or not therapy with Ro 4-1634 diminished the nitroglycerin requirement.

RESULTS

Twenty patients completed the 4 one-month trial periods. From the report cards kept by the patients, a tabulation was made of the total number of nitroglycerin tablets taken by each subject during the 2 drug periods and the total number taken during the 2 placebo periods. These data are presented in Table 1. For reasons previously noted, data for the first ten days of each period were excluded. Included in the table is information regarding the age, sex, and severity of the angina for each patient.

During Ro 4-1634 therapy, 11 subjects required less nitroglycerin; the amount ranged from 33 to 89 per cent of that required during the placebo periods, the average reduction being 67 per cent. Conversely, in 4 subjects the nitroglycerin requirement was increased during Ro 4-1634 therapy, by 22 to 121 per cent, the average increase being 68 per cent. Five subjects reported insignificant changes in the nitroglycerin requirement (less than 10 per cent). The overall reduction in the nitroglycerin requirement during treatment with Ro 4-1634, as compared with the control periods, was statistically significant at the 0.01 level. Further subjective improvement was reported by many of the patients when the daily dose of Ro 4-1634 was increased to 100 mg. or more following completion of the double-blind study.

[1] Kindly supplied by Hoffman-La Roche Inc., Nutley, N. J.

TABLE 1

Clinical Data and Nitroglycerin Requirements for Individual Patients during Therapy with Ro 4-1634 and Placebo

Subject		Severity of Angina	No. of Nitroglycerin Tablets Required*		Change (%)
No.	Age & Sex		During placebo therapy	During Ro 4-1634 therapy	
1	53,F	1+	9	20	+122.2
2	76,M	1+	38	14	−63.2
3	56,M	1+	43	67	+55.8
4	49,F	2+	18	3	−83.3
5	42,M	2+	33	22	−33.3
6	66,M	2+	34	9	−73.5
7	55,F	2+	37	10	−73.0
8	55,F	2+	40	38	−5.0
9	51,M	2+	45	22	−51.1
10	75,M	2+	61	7	−88.5
11	72,F	2+	82	26	−68.3
12	50,M	2+	327	299	−8.6
13	58,M	3+	19	2	−89.5
14	63,F	3+	23	24	+4.3
15	78,M	3+	25	43	+72.0
16	55,M	3+	26	28	+7.7
17	66,M	3+	34	9	−73.5
18	69,M	3+	58	53	−8.6
19	55,M	3+	73	89	+21.9
20	69,M	3+	81	50	−38.3

* Total for the 2 one-month therapeutic trials with each compound.

DISCUSSION

Previous studies by others (6, 7), not conducted in double-blind fashion, have indicated that therapy with Ro 4-1634 favorably affects the symptomatology in cases of angina pectoris. However, somewhat different criteria for evaluating the clinical effectiveness of the drug were employed by these investigators. This may explain the apparent discrepancy between the 29 per cent (Russek) and the 60 per cent (Abrams *et al.*) of "good" or "excellent" response in the two studies. On the other hand, the opinion was uniform that there were virtually no significant side-effects from therapy with Ro 4-1634.

These findings are confirmed in the present study, conducted in a carefully designed double-blind fashion. Eleven of 20 subjects (55 per cent) required less nitroglycerin while receiving 75 mg. of Ro 4-1634 daily; the average reduction was 67 per cent. Analysis of the report cards for subjective evidences of improvement proved to be unsatisfactory, however. Aside from the daily dose of nitroglycerin, the patients frequently omitted clinical data, or recorded them incompletely

Two patients complained of symptoms that might be attributed to the monoamine oxidase inhibitor. One experienced frontal headaches of several days' dura-

tion that subsided spontaneously without change in medication. The other complained of transient dizziness (also present before the study) that was not associated with demonstrable changes in blood pressure. There were no untoward cardiovascular incidents, electrocardiographic changes or abnormal laboratory findings that could be attributed to therapy with Ro 4-1634. Thus the low incidence of side-effects noted in previous reports was borne out by the present study. The lack of side-effects may reflect the relatively weak monoamine oxidase-inhibiting properties (8) of Ro 4-1634. Nevertheless, in the dosage employed in this study (75 mg. per day), less nitroglycerin was required to control the angina; the reduction was statistically significant.

This investigation was planned to yield clinical information with respect to the use of Ro 4-1634 as an adjunct to therapy in cases of angina pectoris. The data provide no clues as to the reasons for the favorable effects observed.

Similar findings were reported at a symposium on Ro 4-1634 held in Lugano, Switzerland (October, 1959) by seven groups of workers who treated a total of 192 patients. Their observations are summarized in Table 2. Improvement was noted in 31 to 90 per cent of these patients, and the incidence of side-effects ranged from 10 to 27 per cent. The side-effects included nausea, drowsiness, insomnia, constipation and dryness of the mouth. However, a wide range of dosage was employed, and many of these admittedly preliminary reports lacked control data. In most instances adverse reactions subsided spontaneously or after reduction in medication.

These previous observations concerning Ro 4-1634 are confirmed by the findings of the present study conducted with cases of angina treated in double-blind fashion.

It is noteworthy that postural hypotension was not observed. This militates against Cesarman's (8) hypothesis that the amelioration of angina is due to a ganglioplegic effect. Moreover, we were unable to attribute the favorable response to changes in mood, as suggested by Master and Donoso (9), because

TABLE 2

Ro 4-1634 Therapy in Angina Pectoris

(Summary of results reported at Symposium, Lugano, Switzerland, October 1959)

Author (1959)	No. of Cases	Dosage of Ro 4-1634 (mg./day)	Results (%)	
			Improvement (good or excellent)	Side-effects
Emanuel, R. A.	35	175–400	31	10
Oblath, R. W.	31	25–200	60	10
Dighiero, J.	45	50	62	11
Aareseth, S.	20	100–150	65	5
Murphy, F. M.	26	150–220	68	27
Suter, L.*	15	150–300	87	14
Dalla Volta, S.	20	150–225	90	10

* Double-blind study.

definite and consistent changes were neither observed by the clinic physician nor reported by the patients. This difference in the action of Ro 4-1634 from that observed with iproniazid may be one of degree. However, equally probable is a qualitative difference that may enhance the usefulness of Ro 4-1634 in cases of angina. On the basis of the available clinical data on Ro 4-1634, further therapeutic trials seem warranted.

SUMMARY

A therapeutic regimen consisting of either 75 mg. daily of the iproniazid analog Ro 4-1634, or a placebo, was tested by the double-blind technique in 20 patients with angina pectoris. Eleven of the 20 subjects required less nitroglycerin while receiving Ro 4-1634; the average reduction in dosage was 67 per cent. The reduction in nitroglycerin requirement during treatment with Ro 4-1634, as compared with the placebo periods, was statistically significant at the 0.01 level.

The use of report cards by the patients for additional data as to the beneficial or adverse effect of therapy proved to be unsatisfactory because the information was often omitted or was incompletely recorded. Clinical appraisal, however, indicated that side-effects were minimal or absent in virtually all subjects. No laboratory evidence of toxicity was observed.

Acknowledgment

We are indebted to Mr. Raymond E. Thomas of the Department of Statistics, George Washington University, for statistical analysis of the data, and to Dr. John M. Evans for helpful suggestions in the preparation of the manuscript.

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MONOAMINE OXIDASE INHIBITORS AND HYPERTENSION*

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The monoamine oxidase (MAO) inhibitors offer a combination of pharmacodynamic activities not found in other available hypotensive agents. They lower the arterial pressure, and at the same time improve the patient's mental outlook and sense of well-being; side-effects are rare, and not severe. Physicians who have treated hypertensive patients with ganglion-blocking agents and reserpine know that these drugs can be tools of the devil. The ganglion-blocking agents in particular, although effective in lowering arterial pressure, also act on the parasympathetic ganglia. They produce such distressing side-effects that the patient often wonders whether he might be better off dead. He is overcome by weakness and fatigue (resembling curare-induced symptoms), loss of sexual potency, blurred vision, anorexia, nausea and vomiting, dry mouth, constipation, bladder atony, and sometimes even pulmonary and neurologic syndromes (1–3).

The side-effects of reserpine, although not usually as severe as those of the ganglion-blocking agents, nevertheless cause discomfort. The patient complains of stuffy nose, weakness and fatigue, and suffers from hyperorexia, insomnia, or restless sleep with nightmares; in extreme cases he may become agitated and acutely depressed (2–4). Physicians with extensive experience in the use of reserpine know that often the best procedure is to discontinue therapy, since immediately afterward the adverse reactions disappear.

It is as desirable to maintain the patient's comfort as to achieve control of the disease. Therefore, it is our hope that the MAO inhibitors hold the key to more effective management of hypertension, with minimal inconvenience due to side-effects.

One of the earliest MAO inhibitors to be used specifically for the control of hypertension was β-phenylisopropyl hydrazine hydrochloride (Catron)[1] Gillespie, Terry and Sjoerdsma (5) used Catron extensively and were enthusiastic over its effect as a depressor in cases of severe hypertensive disease, some with grades 3 and 4 retinopathy. In these cases, medication was started with doses of 6 to 20 mg. per day and the patients were closely followed for six to seven months. The results showed that Catron, either alone or in association with a chlorothiazide-type drug, caused a decrease in the blood pressure, cessation of the hemorrhages in the eyes, and a reduction in heart size. At first the only apparent side-effect was loss of red-green color discrimination in a few patients—a condition which apparently disappeared when therapy was discontinued. Later, however, several cases of retro-optic nerve damage were noted. For obvious reasons, Catron is no longer used in hypertension.

* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November 3, 1960.

[1] Product of Lakeside Laboratories, Inc., Milwaukee, Wisconsin.

TABLE 1

Effect of Nialamide Plus Chlorothiazide on the Mean Arterial Pressure (M.A.P.) (mm. Hg)

Avg. Pre-treatment M.A.P.	Avg. Treatment M.A.P.	Avg. Post-Treatment M.A.P.
235 ± 38	176 ± 24	222 ± 29

CLINICAL STUDY

Another drug which has been fairly well investigated as a hypotensive agent, and with which we have had personal experience, is nialamide (Niamid).[2] We used this agent in 23 patients with severe hypertension, at the District of Columbia General Hospital, Washington, and in 5 patients seen in private practice. The severity of the hypertension should be stressed. The optic fundi showed numerous hemorrhages and exudates; 9 patients had papilledema and 4 had uremia.

The majority of these patients had been previously maintained with ganglion-blocking agents and guanethidine, and the usual disturbing side-effects had occurred. These drugs were stopped, and a combination of nialamide (200 to 300 mg. per day) plus chlorothiazide (500 mg. twice daily) was started. During the first three to four weeks there was no change in arterial pressure. Within a week after initiation of therapy, however whether due to discontinuation of the ganglion-blocking agents or not, the patients began to feel better. After three weeks of therapy a gradual fall in arterial pressure began, which eventually became a true fall, reaching a maximum at the fifth or sixth week. During this time, the fall in mean arterial pressure was 23 per cent—a significant drop (Table 1). Even more significant from the standpoint of both the patients and the doctor was the striking objective and subjective improvement. The hemorrhages cleared up, there was reversion of the papilledema, and the patients claimed they had never felt better in their lives.

Sometime between the ninth and the twelfth weeks of therapy, however, the arterial pressure ceased to fall; increasing the dosage to 300 mg. and 350 mg. per day caused no further lowering of the pressure. It was apparent that we were dealing with drug resistance. As nialamide became progressively ineffective, the arterial pressure began to rise and there was exacerbation of the vascular disturbances; retinal hemorrhages and exudates reappeared, and papilledema recurred.

There may have been some correlation between the dosage levels and the development of resistance. However, further studies with smaller dosages showed that, regardless of the size of the dose, the pattern of activity remained the same, *i.e.*, slow onset of action followed by a distinct intermediate fall in pressure, and then development of drug resistance.

[2] Product of Pfizer Laboratories, Brooklyn, New York.

COMMENT

There is as yet no ideal therapeutic agent for the control of hypertension. Selection of a course of therapy, whether conservative, chemotherapeutic or surgical, is wholly dependent upon the degree of cardiovascular disease and the nature and severity of the symptoms. The state of the optical fundi, the functioning of the heart, and the presence or absence of cardiac hypertrophy and renal malfunction must all be determined before prescribing therapy. Least important in evaluating the disease is the precise blood pressure reading. It is known that a patient may have an extremely high blood pressure, both diastolic and systolic, and yet have very little vascular disease. His major disease may well be supratentorial and he will respond much more readily to reserpine or phenobarbital than to the stronger medications. In fact, the "nervous" patient responds poorly to the stronger drugs but much more favorably to drugs like sodium amytal. The ganglion-blocking agents and guanethidine are best reserved for cases of malignant hypertension and should not be used unless this condition has been definitely diagnosed.

Iproniazid (Marsilid),[3] isocarboxazid (Marplan)[3] and other MAO inhibitors may be used in refractory conditions, but are not recommended as the drugs of choice pending further investigation of their hypotensive action and possible toxicity. Little is known about this group of drugs. No one has yet determined how or why they act as they do, or what untoward reactions may result from extended therapy. The experiences of others, as well as our own, attest to the fact that for a certain length of time after administration there is a marked reduction in the blood pressure as well as diminution in the severity of the vascular disease. On the other hand, drug resistance and sometimes irreversible damage may result after prolonged use of some of the presently available inhibitors. However, the limitations involved in the present-day clinical use of these agents in long-term therapy do not justify their elimination as potentially useful agents in the future. We are continuing our investigations with such drugs as Ro 5-1025, which gives promise of being low in toxicity and slow in action; if so, toxicity and resistance may not be induced even after prolonged administration.

CONCLUSIONS

Monoamine oxidase inhibitors offer invaluable combinations of pharmacodynamic activity. Through more intensive research, greater insight may be gained into the mechanisms of their action. In this way, their clinical effects may be better controlled, and they can be more readily used as euphoric and hypotensive agents.

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AMINE OXIDASE INHIBITORS IN THE TREATMENT OF ESSENTIAL HYPERTENSION*

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The exact role of the amine oxidase inhibitors in the treatment of essential hypertension has not as yet been determined, but data accumulated so far indicate that this group of drugs may at least have a place in adjunctive therapy. We wish to present our experience during the past year with several of the amine oxidase inhibitors in the treatment of hypertension.

CLINICAL STUDY

The study was conducted on 43 patients with essential or arteriosclerotic hypertension who were continuously hospitalized over a nine-month period in a chronic-disease home. For six-week treatment periods, the patients were given either a placebo, reserpine, a barbiturate, or the amine oxidase inhibitor, isocarboxazid (Marplan). Thus treatment was carried out in a cross-over manner, alternating placebos and the other drugs.

In most of the cases, at least one six-week period was devoted to the combined use of reserpine and isocarboxazid. The theory is that reserpine exerts its antihypertensive action by decreasing the levels of peripheral serotonin, noradrenaline and adrenaline. If we assume, on the contrary, that the amine oxidase inhibitors increase the level of peripheral or perhaps central serotonin, noradrenaline and adrenaline, the effect of reserpine might cancel out the effect of the inhibitor.

In an attempt to confirm this theory, the drugs were employed both singly and in combination. The usual initial dosage was 20 mg. per day, increased to 40 mg. per day as the mean level; beyond this dosage the patients did not tolerate the drug well. Most patients responded to 30 or 40 mg. per day.

* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November 3, 1960.

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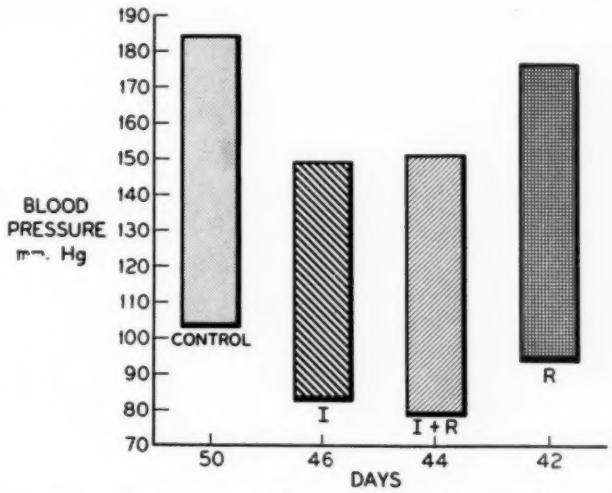

FIG. 1. Blood pressure responses in 25 patients with hypertension. I = isocarboxazid (40 mg. per day); I + R = isocarboxazid in combination with reserpine (0.5 mg. per day); R = reserpine only.

All patients were followed carefully with weekly liver function tests (including serum transaminase levels). During the nine-month period to date, no significant hepatic abnormalities were detected. In 1 patient receiving a derivative of isocarboxazid, there was a transient change in several parameters of liver function; the significance of this finding is not clear.

Side-effects included insomnia, and fairly severe orthostatic hypotension in 3 cases, lasting for several weeks.

Figure 1 shows the response of the blood pressure in 25 patients during the control period of fifty days, and then during treatment with isocarboxazid, isocarboxazid plus reserpine, and reserpine alone. The control range of blood pressure (sitting position) was 185–102 mm. Hg. It may be seen that isocarboxazid alone lowered the pressure to 150–84 mm. Hg, and isocarboxazid plus reserpine lowered it to 152–78 mm.; with reserpine alone, it rose to 152–94 mm. During either form of isocarboxazid therapy, a significant fall in mean blood pressure occurred in the majority of the patients. During the period when reserpine (0.5 mg. per day) was given in combination with isocarboxazid, the additional lowering of the blood pressure was slight, in association with a tendency towards a fall in the mean diastolic level. During the subsequent period of treatment with reserpine alone, the blood pressure returned to a level approximating that noted during the control period. Thus, multiple cross-over experiments showed that reserpine alone was relatively ineffective as compared with isocarboxazid alone. Moreover, reserpine added very little to the effect of isocarboxazid, although there was no antagonism between the action of the two drugs.

Isocarboxazid does not exert its lowering effect upon the blood pressure for five to ten days. Following discontinuation of isocarboxazid therapy, the reduction lasts for seven to twenty days; then the pressure gradually rises, but some-

times does not reach the pre-treatment level for as long as four weeks. Thus there is a marked delay in initiation of the hypotensive effect, and a marked prolongation of action after isocarboxazid is withdrawn.

Two case abstracts illustrate some of the effects we have noted in a large percentage of patients:

Case 1 (Fig. 2). Isocarboxazid (RO 5-0831/1) was administered after a control period of twenty-six days. Each point on the graph in Figure 2 represents the mean blood pressure for three consecutive days. The fall began approximately three days after isocarboxazid was started but did not reach its maximum for several weeks, after which a plateau was maintained. During placebo medication, there was a distinct delay before the blood pressure returned to the pre-treatment level. Following this, reserpine (0.25 mg. twice daily) was administered but had almost no effect on the blood pressure. A combination of amine oxidase inhibitor and reserpine produced another significant fall in blood pressure. After discontinuation of all medication, the pressure promptly returned to the pre-treatment level.

Case 2 (Fig. 3). In this patient a definite response was noted during placebo medication (observed also in a small percentage of the other patients). A further drop in blood pressure was noted when the amine oxidase inhibitor, isocarboxazid (Marplan), was employed. There was no change when reserpine was added, but neither was there any evidence to indicate a "blocking effect" of reserpine on isocarboxazid. During treatment with reserpine alone, the blood pressure rose promptly, and reached the pre-treatment level shortly after discontinuation of all medication. Blood pressure during the maximal drug effect was considerably lower than ordinarily desired.

When chlorothiazide or one of its derivatives was used in combination with isocarboxazid, the lowering of blood pressure was achieved more smoothly.

Isocarboxazid and two of its derivatives were used in a larger series of patients who were not as carefully controlled as the foregoing series. To date,

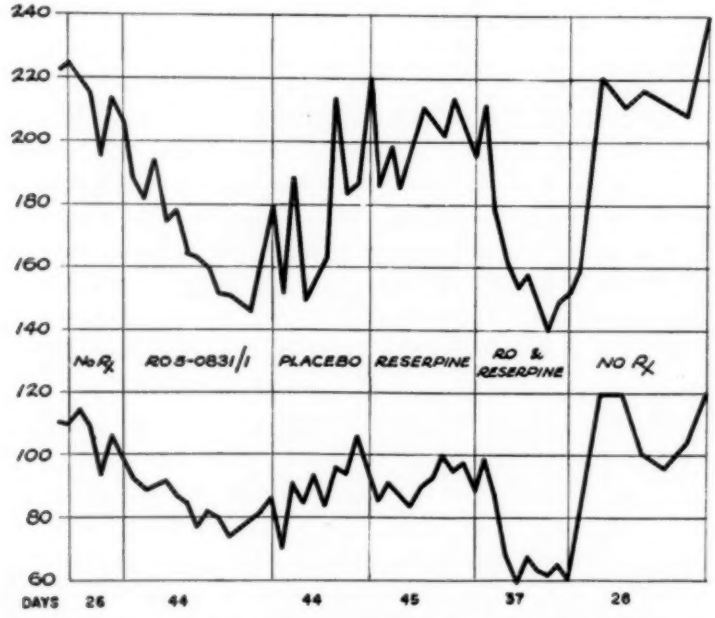

FIG. 2. *Case 1.* Response of the blood pressure in a 68-year-old woman to isocarboxazid (RO 5-0831/1), placebo, reserpine, and a combination of isocarboxazid and reserpine.

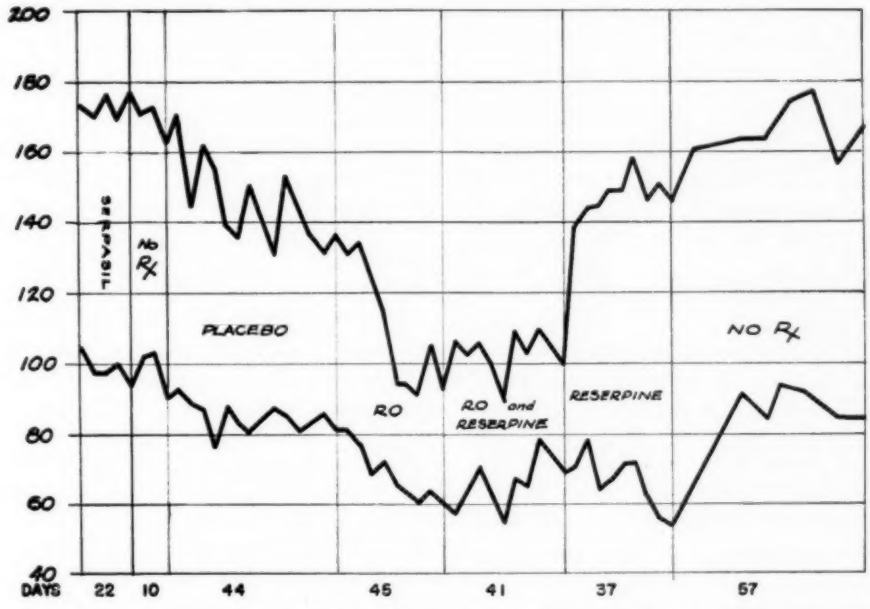

FIG. 3. *Case 2.* Response of the blood pressure in a 70-year-old woman to placebo, isocarboxazid (RO), a combination of isocarboxazid and reserpine, and reserpine alone.

our over-all results indicate that this group of drugs may eventually have a place in the treatment of cases of severe hypertension in which several drugs have to be employed—for example, in patients who are receiving reserpine and a chlorothiazide derivative without any hypotensive effect, and in whom an additional drug is needed in order to achieve satisfactory lowering of the blood pressure. In these severe cases, hydralazine (Apresoline) may be chosen for the third drug; it may be that one of the amine oxidase inhibitors may also prove satisfactory for long-term treatment. Amine oxidase inhibitors are not nearly as potent as the ganglion blockers or the newer peripheral sympathetic blockers such as bretyllium or guanethidine. However, they may have a place, in combination with reserpine and chlorothiazide, in the treatment of moderately severe cases of hypertension.

When nialamide was used to lower the blood pressure, drug tolerance developed. Nialamide did not appear to be as effective as isocarboxazid in the treatment of hypertension; only 2 patients showed a continuously good response.

In our amine oxidase series of hypertensive patients, a single death occurred following coronary occlusion. Any relationship to the amine oxidase therapy is speculative. At the time of death, the patient's blood pressure had been lowered significantly, but not to hypotensive levels.

DISCUSSION

DR. RUSSEK: Dr. Moser, do you use these drugs in your office patients with hypertension and angina pectoris?

DR. MOSER: Yes, I certainly do. Before answering that more fully, I should like to disagree very heartily with Dr. Finnerty. Dr. Finnerty probably would treat a patient with a

diastolic blood pressure persistently over 100 mm., particularly if the patient were a male and had any evidence of cardiovascular disease.

By the treatment of hypertension we usually mean sedation (with reserpine if there is no history of a previous depression or gastric ulcer) and diuresis (with agents such as chlorothiazide or any one of its derivatives). There is enough evidence from studies on animals and human subjects to show that by merely lowering the blood pressure (a parameter of vascular involvement that we are able to measure), some of the secondary vascular changes associated with severe hypertension can be reversed. Inferentially, there is "beginning" evidence (not enough time has elapsed since the development of effective treatment) that, at least in males, the diastolic blood pressure can be lowered and possibly some of the secondary vascular changes prevented. I would therefore differ with Dr. Finnerty, and I would use these drugs to treat a patient with a persistent diastolic elevation of blood pressure. With the present state of our knowledge, I would not begin with ganglion blockers, nor would I use the amine oxidase inhibitors unless other drugs such as reserpine, chlorothiazide and even hydralazine did not work. However, in the more severe cases, I would employ all or any of the drugs in combination.

I use amine oxidase inhibitors in office patients, in just the way I have outlined. If the patient does not respond to the drugs that we know most about, *i.e.*, hydralazine, reserpine, chlorothiazide and derivatives, I do not hesitate to use amine oxidase inhibitors. This is a safe group of drugs—at least those we have talked about here today. Some of the derivatives may produce secondary hepatic changes, but so far in our experience of over a year, we have rarely seen any significant side-effects from amine oxidase inhibitors.

DR. FINNERTY: May I defend my point by saying that it is not that the blood pressure should not be lowered in patients without vascular disease or with very little vascular disease. My point was that the blood pressure can be much more effectively lowered by drugs such as reserpine or sodium amytal, because in these patients the disease is predominantly supratentorial.

DR. RUSSEK: Dr. Moser, in your study, did the supine blood pressure fall, and how long have your patients been followed?

DR. MOSER: In the study referred to this morning, the supine blood pressure did not fall in the majority of patients. About one-third of the patients did experience a significant fall in blood pressure when in the supine position, but this occurred after a prolonged period of regulation of the pressure in the sitting and standing positions. It often took from three to four weeks for the supine pressure to fall. We do not know whether this was a secondary effect or a drug effect.

The patients reported were followed in the hospital continuously for a period of nine months. We did not observe any tolerance to isocarboxazid corresponding to the tolerance to nialamide observed by Dr. Finnerty. This drug, another of the amine oxidase inhibitors, is effective in psychic disorders.

SUMMARY OF PANEL DISCUSSION ON CLINICAL APPLICATION OF AMINE OXIDASE INHIBITORS IN ANGINA PECTORIS AND HYPERTENSION

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The amine oxidase inhibitors appear to add a new dimension to the treatment of angina pectoris. Some of these preparations are effective in reducing the severity and frequency of anginal episodes in well over 50 per cent of the

patients treated. Several years ago, Dr. Pletscher demonstrated that in any series of hydrazine derivatives the therapeutic efficacy as well as the degree of toxicity of a given agent is related to its potency as an inhibitor of amine oxidase, and this appears to stand up in the course of clinical study. Thus, the greater the therapeutic efficacy of a given drug, the greater will be the likelihood of side-effects.

The mode of action of the amine oxidase inhibitors is still unknown, but it would appear that, at least in angina pectoris, they block painful stimuli from the heart to the central nervous system. They apparently influence the neuralgic manifestations of myocardial ischemia without influencing the local myocardial anoxia that evokes it. Nevertheless, the discomfort in angina pectoris is frequently out of proportion to the underlying myocardial ischemia; consequently, symptomatic relief may greatly reduce disability and improve exercise tolerance. Thus, amine oxidase inhibitors constitute an unmistakable advance in the treatment of angina pectoris, and they are clearly indicated in the treatment of severe and intractable cases, particularly when other measures have failed. The introduction of amine oxidase inhibitors in therapy has also reduced the need for ablation of the thyroid by radioactive iodine and for surgical operations which allegedly increase coronary blood flow.

In hypertension, there is the possibility that amine oxidase inhibitors may find a place as adjunctive medication. In the future, new agents may be found to fill the wide therapeutic gap between reserpine, hydrochlorothiazide and hydralazine on the one hand and ganglion-blocking agents on the other.

We should like to take this opportunity to thank the members of the panel for their contributions to this symposium.

PANEL DISCUSSION ON THE USE OF ENZYMES IN THE DIAGNOSIS OF HEART DISEASE*

Moderator: HOWARD E. TICKTIN, M.D., Chief Medical Officer, George Washington University Medical Division at D. C. General Hospital; Assistant Clinical Professor of Medicine, George Washington University School of Medicine, Washington, D. C.

Panelists: FELIX WRÓBLEWSKI, M.D., Associate Professor of Clinical Medicine, Cornell University Medical College, New York City.

WARREN E. C. WACKER, M.D., Associate in Medicine, Harvard Medical School; Associate in Medicine, Peter Bent Brigham Hospital, Boston, Massachusetts; Investigator, Howard Hughes Medical Institute.

MODERATOR TICKTIN: I should like to introduce our panel members: Dr. Felix Wróblewski, who is familiar to you because of his original investigative work in the field of clinical enzymology, and Dr. Warren Wacker, who has had broad experience in the general field of enzyme kinetics and their clinical applications.

The subject of enzymes in the diagnosis of heart disease has drawn a great deal of attention in the literature in the last five or six years. The impetus given this work probably stems from the observations of Drs. Wróblewski, La Due and Karmen on serum transaminases in acute myocardial infarction. Since that time, observations on the alterations of serum enzyme activity in various diseases have multiplied rapidly. There is now a vast accumulation of data on any number of enzymes with respect to the changes noted in various cardiac and noncardiac disorders.

We shall restrict the subject of this discussion to the use of enzyme determinations in the diagnosis of heart disease. Within this framework, and because of time limitations, we shall try to restrict ourselves further to a discussion of just a few of these numerous enzymes—specifically, transaminases [serum glutamic oxalacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT)] and lactic dehydrogenase (LDH). Even in smaller community hospitals, determination of SGOT activity has become a routine laboratory procedure in the diagnosis of acute myocardial infarction, just as the determination of serum amylase activity has become a routine measure for the diagnosis of acute pancreatitis.

For some time it has been known that anterior chest pain in association with a rise in activity of serum transaminase is not necessarily an indication of acute myocardial infarction. It is noteworthy that changes in the serum transaminase level are not specific for this disease, as these enzymes are present in most tissues of the body. Alterations in enzyme activity, when taken out of the clinical context, are difficult to interpret.

I shall now ask Dr. Wróblewski to comment on *the mechanism involved in the rise of serum transaminase and lactic dehydrogenase activity in myocardial infarction, and possibly in some other disorders for which these enzyme levels are used diagnostically.*

* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November 3, 1960.

DR. WRÓBLEWSKI: The changes in serum enzyme activity noted in patients with myocardial infarction are primarily a reflection of the release of intracellular enzyme into the circulating plasma. Regardless of whether or not a component is contributed by the liver (*e.g.*, in association with congestive hepatomegaly), the major component is derived from the intracellular release of these enzymes from heart tissue. This, however, does not imply that the same mechanism plays a role in other diseases that are quite dissimilar pathophysiologically from myocardial infarction. In liver disease (both cirrhosis and hepatitis), dermatomyositis and other disorders, the elevated level of serum enzymes is sometimes produced by a mechanism quite different from that in myocardial infarction.

In noncardiac disorders, the cause of the increased serum level appears to be increased elaboration, rather than release of these enzymes from the intracellular components associated with necrosis. There is an important difference between the pathophysiologic mechanisms in myocardial infarction and in diseases of extracardiac origin.

DR. TICKTIN: Dr. Wróblewski, in view of the presently accepted concept that the elevated serum enzyme level in acute myocardial infarction is due to liberation of enzymes from necrotic cardiac tissue, *can the size of the infarct be estimated fairly accurately from the degree of elevation in the serum enzyme level in a given patient?*

DR. WRÓBLEWSKI: Apparently I did not make myself entirely clear. Not all the enzymes necessarily come from the necrotic cardiac cells. They may also come from adjacent non-necrotic cells in which (due to hypoxia and so forth) permeability is altered enough to permit the release of intracellular enzymes. Nevertheless, though not all the enzymes released in myocardial infarction are derived from necrotic cells, all presumably come from intracellular areas—some consisting of necrotic cells, but some consisting of adjacent intact cells in which the permeability of the cell membrane has been compromised.

A relationship between the size of the infarct and the height of the serum enzyme level can be demonstrated in dogs. So far, however, it has not been established in human subjects, although it has been observed in some cases. I would not care to make such an estimate on the basis of the serum enzyme changes, in any one case. This represents a conclusion based on a mosaic of clinical and laboratory factors.

DR. TICKTIN: *It has been stated in the literature that elevation of serum enzyme activity above a level of 350–400 units in uncomplicated myocardial infarction is an ominous prognostic sign. Do you agree?*

DR. WRÓBLEWSKI: It is probably true. It should be emphasized, however, that these patients frequently have pulmonary edema and are in a state of shock. All the other clinical and laboratory signs which indicate a poor prognosis are present. To conclude that the poor prognosis is based solely on the high level of serum enzyme activity is to overlook all of the other factors. Medical literature, like political literature, is sometimes misleading.

DR. TICKTIN: Dr. Wacker, if you undertook the management of a patient with acute anterior chest pain in an institution where serum transaminase and lactic dehydrogenase activity could be readily determined, *when would you order*

enzyme tests with reference to the onset of the illness, and how frequently should they be performed? If the tests had to be restricted to one particular enzyme, which one would you choose?

DR. WACKER: The duration of the elevations in serum transaminase and LDH are fairly well established. Both concentrations rise abruptly after the infarction, reaching a maximum on the first or second day. The transaminase level tends to return to normal within four or five days, whereas the LDH level is elevated for a longer period—about six or seven days. For both, the time pattern of the elevation is specific, *i.e.*, the abrupt rise on the first or second day and the gradual return to normal. This is an important consideration. If a patient has chest pain and you are trying to determine whether he has myocardial infarction, not only is the level of enzyme activity important, but also its time pattern. Therefore, determinations should be made on the first, second and third days after onset of the illness; LDH activity may still be elevated up to seven days after onset. This information may be very helpful in diagnosis.

I have no strong opinions regarding the superiority of any one enzyme test. LDH kinetics are simple and the test is easy to perform. Purely on a technical basis, under routine conditions there may be less danger of a false result with the LDH assay than with the transaminase assay.

DR. TICKTIN: Dr. Wróblewski, *do you have a preference regarding these two enzyme assays in the patient with acute anterior chest pain?*

DR. WRÓBLEWSKI: My experience is somewhat like that of Dr. Wacker; the two tests are about equal in advantages and disadvantages.

DR. WACKER: Dr. Wróblewski measures the LDH in one direction and I measure it in another. Perhaps if he would use the forward reaction he would find fewer disadvantages than when using the backward reaction.

DR. TICKTIN: Would you please explain the two reactions.

DR. WACKER: It is a matter of technical enzymology—kinetics. Moving from pyruvate to lactate is more complicated and troublesome than moving from lactate to pyruvate. Otherwise, if performed under the same circumstances, the tests are comparable.

DR. TICKTIN: Dr. Wróblewski, would you discuss *the problem of the "false positive" result for the transaminase assay in the patient with anterior chest pain, and give some of the reasons for these false results.*

DR. WRÓBLEWSKI: It has become increasingly clear that enzyme tests in myocardial infarction have decided limitations. These limitations include the very point to which Dr. Ticktin referred, namely, that in many conditions other than myocardial infarction enzyme changes occur that may easily be confused with those accompanying myocardial infarction.

What are these factors? One is the influence of drugs—for example, the phenothiazines, the opiates administered to patients with chronic biliary-tract or pancreatic disease, or large doses of anticoagulants like warfarin (Coumadin) in patients with congestive hepatomegaly or underlying cirrhosis. Indeed, any conceivable drug might have some effect on these enzymes through a subtle, not readily discernible, hepatotoxic action. Therefore, any drug used in the patient

with either suspected or actual myocardial infarction may contribute to raising the serum enzyme level above the normal range.

The presence of shock, resulting in minimal central lobular necrosis of the liver, profound hypoxia of the peripheral muscles, or pulmonary infarction may cause a rise in serum enzyme activity. There is some evidence that the hypoxia due to long-standing arrhythmias, in the absence of discernible histologic evidence of necrosis in the myocardium, may induce liberation of enzymes from intact cells.

The physician must also be aware that pancreatitis, electrocardiographically and clinically, sometimes mimics coronary insufficiency or even subendocardial infarction. In the latter conditions the serum enzyme level may be elevated, adding to the difficulties in differential diagnosis.

Renal infarction and splenic infarction fortunately are not too common in the clinical setting of suspected coronary insufficiency. If one adds to the list such sophisticated diagnoses as aortic aneurysm and pericarditis, it may be seen that there are so many opportunities for confusion that all enzyme determinations in suspected cases of myocardial infarction or coronary insufficiency must be interpreted with great care. *Many extracardiac factors can confuse the evaluation of enzyme activity.* It is worth emphasizing, even to a group oriented to these problems, that the diagnostic use of enzyme determinations in cases of suspected myocardial infarction has distinct limitations. These limitations can cause confusion and difficulty in the diagnosis and management of such cases.

DR. TICKTIN: Dr. Wróblewski, *since we emphasize the need for serial blood sampling, does the resulting curve of serum enzyme activity help in differentiating some of these non-myocardial causes of enzyme elevation?*

DR. WRÓBLEWSKI: The curves are helpful when it is known that an infarct is present, but often the diagnosis cannot be established. The enzyme changes are most useful when the diagnosis is not clear, or when the opportunity for serial blood sampling occurs soon after the onset of symptoms. (The patient may come under observation at various periods in the course of his suspected coronary occlusion.) It is true that the curve may help to make the diagnostic conclusions from the enzyme studies more definitive. On the other hand, when reliance is placed just on SGOT and LDH curves, the curve obtained following a suspected or small infarction is sometimes similar to that obtained in diseases such as pancreatitis or acute biliary-tract obstruction. Dr. Ticktin's point is therefore worth emphasizing, namely, that the enzyme curve derived from serial determinations may help to eliminate some, but by no means all, the disadvantages of such tests.

DR. TICKTIN: Dr. Wacker, *do you think that the LDH determination is superior in this situation?* For one thing, the serum LDH level remains elevated longer and thereby gives us more of an opportunity to obtain samples after an infarction has occurred. Is that correct?

DR. WACKER: Yes, in general. However, I should like to add another item. One of the greatest areas of usefulness for these enzyme assays is in ruling out the diagnosis of myocardial infarction. The percentage of patients with proven myocardial infarction in whom there is also a rise in serum enzyme activity, ap-

proaches 100. In our series of 99 patients it was virtually 100 per cent, and in Dr. Ticktin's larger series, in which the glutamic oxalacetic transaminase test was used, it approached 98 per cent.

This gives assurance that the diagnosis of infarction can be fairly well excluded in cases of chest pain without a rise in the serum enzyme level within six days following onset of symptoms.

DR. WRÓBLEWSKI: I should like to comment on that. Dr. Wacker probably would be the first to concede that one can never rule out a diagnosis clinically on the basis of any laboratory finding, positive or negative. I can show you several examples of normal transaminase and lactic dehydrogenase activity in patients who, at the time of postmortem histologic examination, manifested evidence of myocardial infarction.

The difficulty in estimating the time of onset of coronary occlusion in a human subject, as compared with a dog for example, is sometimes quite a problem. Symptoms may not be precisely related to the time of onset of a coronary occlusion. A patient may have some vague complaints which he disregards, but a week later he is suddenly found to have pulmonary edema. The onset of pulmonary edema is not the onset of coronary occlusion; heart failure may occur days, weeks, indeed months, after infarction. The electrocardiogram often does not pinpoint the onset of an occlusion. Let us assume that a patient has symptoms suggestive of occlusion on a certain day, and that on the following day serum enzyme activity is normal. This would not for a moment allow me to exclude the diagnosis of a coronary occlusion that may have occurred a week previously.

Negative laboratory findings of any kind, let alone of enzymes, should never be the deciding factor in excluding any diagnosis, especially that of coronary occlusion.

DR. WACKER: I agree with everything you say, but I should specify exactly what I mean, so that there will be no misunderstanding. We have found with the LDH test, and I think Dr. Ticktin has found with the transaminase test, that if serial determinations are carried out within the specified period of time following infarction, serum enzyme activity is elevated. In our study we established the diagnosis of myocardial infarction with complete accuracy in 99 patients (33 per cent by postmortem examinations and 66 per cent by the classic electrocardiographic changes of myocardial infarction) and all of them exhibited an elevation of serum enzyme activity. Mathematically, the chance of the one hundredth patient showing no rise in enzyme activity is extremely remote.

DR. TICKTIN: Dr. Wróblewski, would you emphasize or elaborate on a point you made previously regarding *enzyme activity following the administration of anticoagulants*. Since we use anticoagulants so much in the treatment of myocardial infarction, this is of practical importance.

DR. WRÓBLEWSKI: Patients with congestive hepatomegaly and patients with underlying liver disease of the cicatricial or of the occult neoplastic type, in the absence of myocardial infarction, show appreciable changes in serum enzyme levels following administration of coumarin derivatives.

Moreover, even in those patients with myocardial infarction who con-

comitantly have congestive hepatomegaly or some quiescent form of underlying chronic liver disease, enzyme changes due to extracardiac factors may be algebraically summated or superimposed on enzyme changes accruing from the infarcted myocardial cell. Thus it is true that in a limited number of situations, but more commonly than is generally recognized, sizable priming doses of coumarin-like drugs will cause enzyme changes either independent of, or added onto those associated with myocardial infarction.

DR. TICKTIN: I should like to change the method of our presentation and ask Dr. Wacker if he would tell us about his *observations on lactic dehydrogenase following pulmonary embolism and/or infarction.*

DR. WACKER: One of the major problems in the use of enzyme assays diagnostically is that of specificity—a point which has been covered in the early part of this discussion. A rise in the activity of any enzyme in serum does not offer a means for specific diagnosis, with the possible exception of the acid phosphatase level in carcinoma of the prostate. However, the technical simplicity of serum enzyme assays and their extreme sensitivity provide the motivation to search for a means whereby they *can* be rendered more specific.

In the course of our studies on myocardial infarction, we uncovered the fact that pulmonary infarction is also associated with a rise in serum LDH activity. In attempting to define this further, we encountered the usual difficulty in studying pulmonary infarction—that of diagnosis. An accurate diagnosis is essential in order to establish any alteration of enzyme activity in a disease.

The usual diagnostic accuracy in pulmonary infarction, using every means available, is about 50 per cent. This inaccuracy is reflected in the very high incidence of unsuspected pulmonary infarction and embolization found at autopsy In our hospital, the diagnosis of pulmonary embolus or infarction is made before death in about 20 per cent of the total number of autopsy cases—a figure which is close to the country-wide average.

For a study of LDH activity in pulmonary infarction, an accurate diagnosis is necessary in the first place. Since this tends to restrict selection to autopsy cases, the question arises whether it is feasible to establish a set of criteria that will insure an accurate diagnosis clinically. In our series this proved to be possible when the criteria represented the most complete clinical picture attainable, as judged by observations on chest pain, hemoptysis, infiltration (x-ray examination), consolidation (physical examination) electrocardiographic changes, an elevated white blood cell count and an elevated serum bilirubin concentration. On the basis of such findings, the diagnosis of pulmonary infarction can be made with an accuracy of 90 per cent.

We studied 17 patients with proven pulmonary infarction or embolization and found elevated serum LDH activity in each. The time course of the elevated serum LDH activity is shown in Figure 1. The activity rose to a maximum within two or three days after the embolization and then gradually returned to normal seven to ten days later. Thus, the time course was similar to that for the elevated serum LDH activity noted after acute myocardial infarction.

Since one of the most frequent problems in differential diagnosis is that of myo-

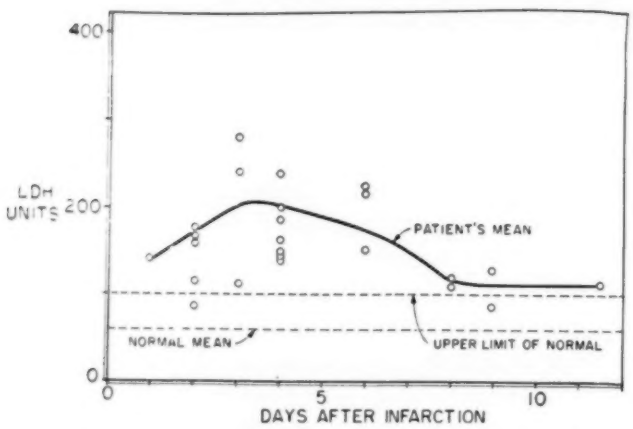

FIG. 1. The course of serum LDH activity in 17 patients with pulmonary infarction or embolism.

cardial infarction versus pulmonary infarction, an elevated serum LDH activity, by itself, does not aid in the differentiation. In order to render this finding more specific, it must be combined with other objective changes to produce a unique diagnostic constellation typical of pulmonary infarction.

In an effort to accomplish this, we studied the serum glutamic oxalacetic transaminase (SGOT) activity in patients with pulmonary infarction, and found that the SGOT level is *not* generally increased as a result of pulmonary embolism or infarction. This is illustrated by Table 1, which shows the serial LDH and SGOT activities in the serum of a 74-year-old man who died of pulmonary embolism. The LDH activity was consistently elevated while the SGOT level remained within the normal range. Another example of the divergence of serum LDH and SGOT activities in a patient with a clinically proved pulmonary infarct, is shown in Table 2. In addition to the increased level of serum LDH, there was also an abnormally elevated level of serum bilirubin.

Table 3 is a summary of the serial LDH and SGOT measurements on the sera of 10 patients with pulmonary embolism or infarction, showing the means and ranges. The serum LDH activity was significantly elevated, ranging from 260 to 415 units (the upper limit of normal is 170 units). In contrast, SGOT activity was within the normal range.

Pneumonia is another disease which frequently must be differentiated from pulmonary infarction. Serum LDH and SGOT activities (means and ranges) in 8 patients with proven pneumococcal pneumonia are shown in Table 4; the levels were normal in all cases.

In summary,[1] the finding of elevated serum LDH activity, normal SGOT activity and elevated serum bilirubin concentration in a patient with cardiac or pulmonary symptoms strongly suggests the diagnosis of pulmonary embolus or infarction.

[1] This work was performed in collaboration with Drs. Miriam B. Rosenthal and Phillip J. Snodgrass and was supported by the Greater Lynn Chapter of the Massachusetts Heart Association.

TABLE 1

LDH and GOT Activities of Serum from a Patient with Pulmonary Embolism

Patient L. C., aged 74 (male). Clinical picture: Dyspnea, pleuritic chest pain, elevation of the left hemidiaphragm.

Autopsy diagnosis: Bilateral pulmonary emboli, phlebothrombosis of the left femoral and popliteal veins.

Days after Onset of Pain	Serum LDH Activity (units)	SGOT Activity (units)
2	190	8
4	195	12
5	180	15

TABLE 2

Serum LDH, GOT and Bilirubin Levels in a Patient with Acute Cor Pulmonale

F. C., aged 56 (male). Pleuritic chest pain and hemoptysis; x-ray examination showed atelectasis and consolidation; ECG diagnosis, acute cor pulmonale.

Days after Onset of Chest Pain	Serum LDH Activity (units)	SGOT Activity(units)	Serum Bilirubin Concentration (mg./100 ml.)
2	400	22	—
3	300	18	—
5	360	21	0.9
6	410	20	—
8	405	20	0.9
10	420	10	1.0

TABLE 3

LDH and GOT Activities in the Sera of 10 Patients with Pulmonary Infarcts

	Serum LDH Activity (units)	SGOT Activity (units)
Mean	310	28
Range	260–415	18–35

TABLE 4

LDH and GOT Activities in the Sera of 8 Patients with Pneumonia

	Serum LDH Activity (units)	SGOT Activity (units)
Mean	140	21
Range	80–160	19–23

DR. TICKTIN: Dr. Wróblewski, have you any comment on Dr. Wacker's presentation?

DR. WRÓBLEWSKI: I should like to ask Dr. Wacker a question. Since many patients with myocardial infarction have concomitant pulmonary embolism with

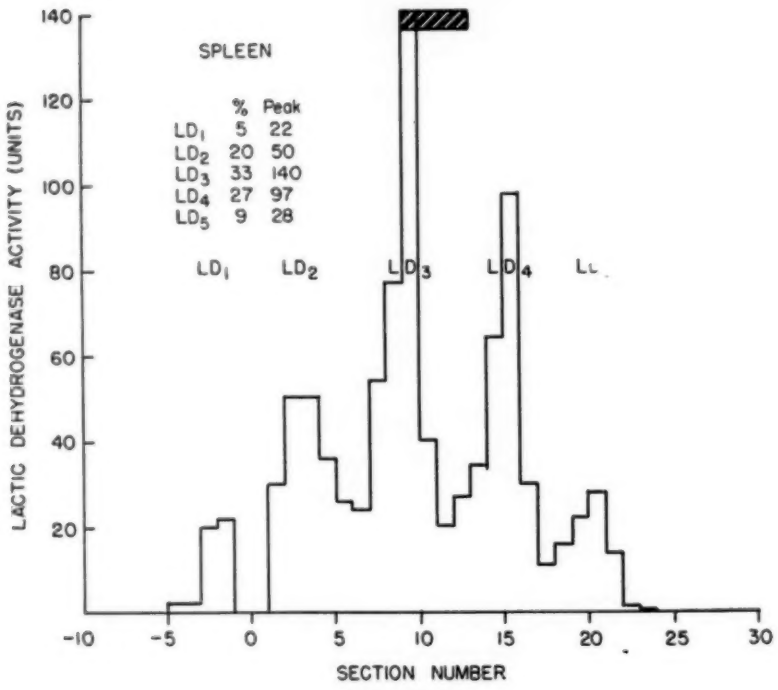

FIGURE 2

or without infarction, how does this clinical experience bear on your observations?

DR. WACKER: No cases of this type were included in our series. So far as I know, none of the patients had myocardial infarction. I recently studied one patient whose serum enzyme activity followed the pattern usually found in myocardial infarction, with a rise in both LDH and SGOT. Subsequently, chest pain developed and the clinical picture was consistent with typical pulmonary infarction; there was a rise in LDH activity but no rise in the SGOT level.

DR. TICKTIN: Thank you, Dr. Wacker. We have also followed a group of patients with pneumococcal pneumonia. Our experience with uncomplicated pneumococcal pneumonia was similar to yours. However, in several patients who were jaundiced in association with pneumococcal pneumonia, there was a rise in SGOT activity.

Continuing with the subject of lactic dehydrogenase, Dr. Wróblewski, would you tell us something about the *most recent and interesting data you have collected on the iso-enzymes of lactic dehydrogenase.*

DR. WRÓBLEWSKI: Hitherto, most of us have thought of enzymes in the plasma and indeed in the tissues as being homogeneous and individual. We think of lactic dehydrogenase, alkaline phosphatase, or amylase as specific enzymes. Enzymes in the plasma, as we measure them, are individual components in total activity, but it is now becoming clear that that is not entirely so. These individual enzymes are in turn made up of components, and what we have been measuring is the algebraic summation of these components.

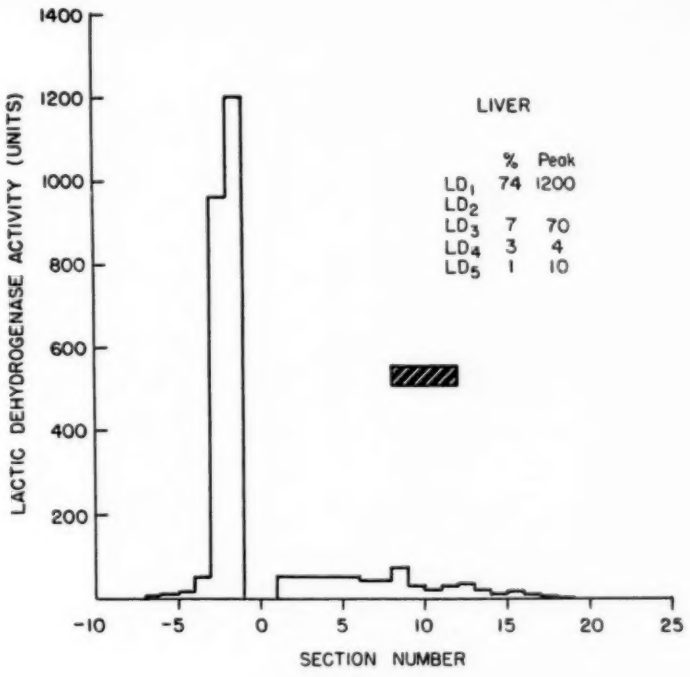

FIGURE 3

Lactic dehydrogenase in the human subject consists of at least 5 individual components which are not readily differentiable by the methods usually employed in clinical laboratories. However, hidden in the total activity is the individual activity of each component. These components, since they are similar, are called iso-enzymes.

The method employed for measurement is a starch-gel electrophoresis. This technique is not new and neither are these observations particularly new, since knowledge of the subject goes back several years.

Figure 2 represents data obtained from the electrophoresis (on starch-gel sheets) of an extract of an homogenized human tissue. The procedure is somewhat analogous to paper electrophoresis of plasma proteins, but instead of measuring the protein components we measure the enzyme components of the tissue being assayed. The cross-hatched rectangle at the top of the figure represents a standard consisting of bovine crystalline hemoglobin; this is used as an aid in locating the peaks. An electrophoretic study of the lactic dehydrogenase in an aqueous extract of normal human spleen (total LHD activity 2,000 units per millimeter) shows that there are 5 components. We have arbitrarily designated them as 1, 2, 3, 4 and 5. The first one migrates away from the focus (to the left) at which the plasma was put into the electrophoretic set-up, and is marked by zero. Thus, when we put an extract of spleen tissue (or plasma) at zero, we can measure these 5 components. In the spleen there is a preponderance of component 3 and proportionally lesser amounts of the others.

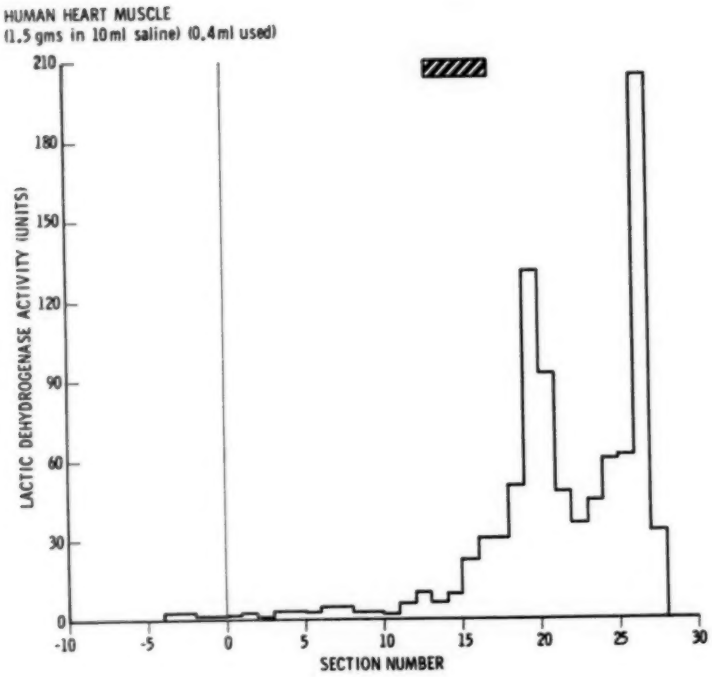

FIGURE 4

In Figure 3 are observations made with an extract of normal human liver. It can be seen that the human liver contains primarily component 1.

Figure 4 shows the LHD composition of an extract of normal human heart muscle, consisting primarily of components 4 and 5. The pattern is different from that for the liver, and readily distinguishable from that for the spleen.

The pattern for the lung (Fig. 5) may seem somewhat similar to that for the spleen; however, the spleen does not contain equal amounts of components 2 and 3. There is certainly no basis for confusion with the patterns for heart muscle or liver. These components of the total activity of lactic hydrogenase in aqueous extracts of normal human tissues help us to identify these organs biochemically with a degree of specificity that approaches that of the familiar histomorphologic method.

Figure 6 shows the total lactic dehydrogenase activity of the plasma of a normal male adult. Characteristically, normal plasma contains all of the 5 LHD components, although occasionally component 2 is missing. As a rule, the preponderant component is 4, with lesser amounts of 5, 3, 1 and 2, in that order.

Compared with the foregoing, the LHD components observed in the plasma of a patient with myocardial infarction are illustrated in Figure 7. This patient was observed on the seventh day following a coronary occlusion, at which time the total activity of lactic dehydrogenase was 744 units. In our laboratory, anything above 400 units is considered abnormal. The transaminase activity was 30, which is normal.

On the other hand, this diagram resembles the one in Figure 4 representing

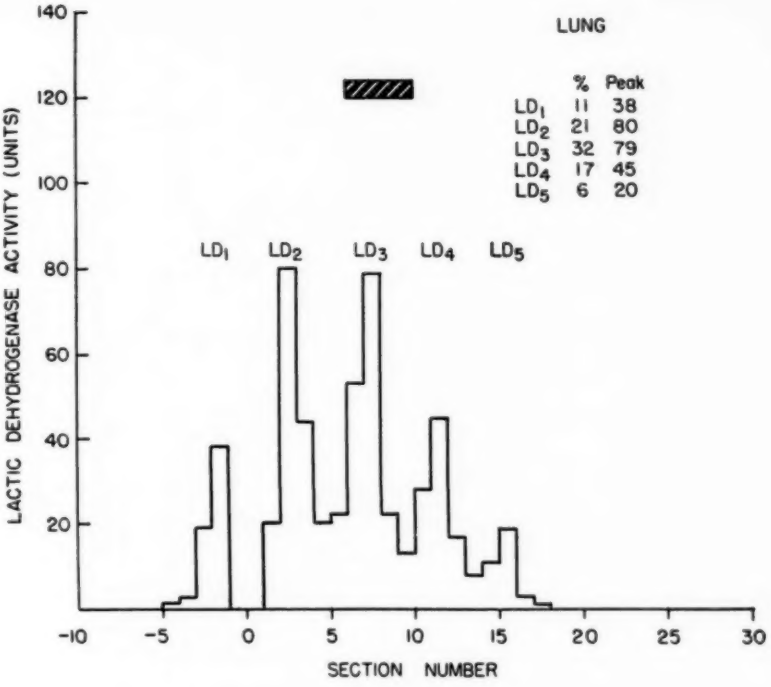

FIGURE 5

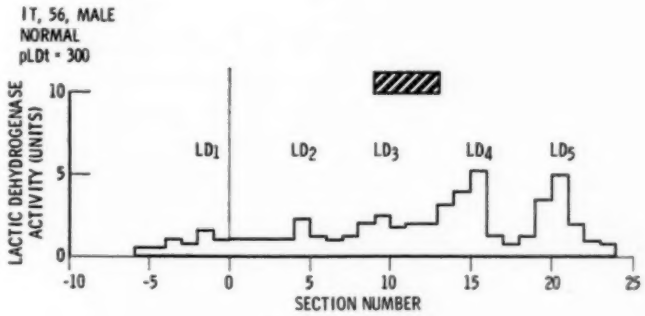

FIGURE 6

the aqueous extract of heart muscle. In a sense, it is as if biochemically, we were detecting pieces of heart muscle in the plasma. The level of total activity, whether elevated or normal, is not of first importance; the most pertinent factor is the pattern, which is that of tissue containing chiefly components 4 and 5. These components, when added to the plasma, distort the plasma pattern so that it resembles the pattern for extract of normal heart muscle.

Figure 8 represents data on another patient with myocardial infarction. It can be seen that on the sixth, seventh, eighth and eleventh day, the pattern was typical of that observed in patients with myocardial infarction. No two human tissues that we have studied contain the same amounts of each LHD component, and no other tissue but heart muscle could have distorted the iso-enzyme components in plasma in this fashion. It is interesting, that even on the twenty-

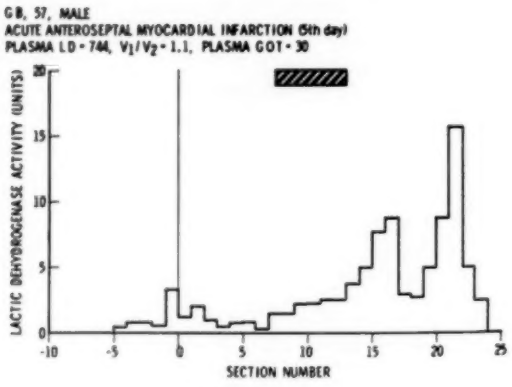
GB, 57, MALE
ACUTE ANTEROSEPTAL MYOCARDIAL INFARCTION (5th day)
PLASMA LD = 744, V1/V2 = 1.1, PLASMA GOT = 30
LACTIC DEHYDROGENASE ACTIVITY (UNITS)
SECTION NUMBER

FIGURE 7

seventh day following the coronary occlusion, some of the abnormal iso-enzyme levels persisted, reflecting the presence of infarcted tissue. Therefore, this iso-enzyme technique helps us to detect infarction at a period when the total serum LHD activity has returned to normal although some of the components may still be present in abnormal amounts.

Why do these iso-enzymes persist at abnormal levels for a long period of time? There is no clear explanation at present, but apparently the homeostatic mechanisms which control the total enzyme activity and tend to lower it to the normal range, "disregard" the components.

Figure 8 represents data on a patient with a subendocardial infarction. I need hardly mention the difficulty in reaching the diagnosis of subendocardial infarction, regardless of the criteria used, since many patients with subendocardial ischemia and infarction are in a state of shock. In this case, a cystoscopy had been performed, and shock ensued. The electrocardiogram showed the characteristic changes. The total plasma transaminase activity remained normal; the lactic dehydrogenase activity rose on the fourth day, but was almost back to normal on the eleventh day. During this period the patient remained in a state of shock and it was difficult to evaluate these total enzyme values, but the patterns were typical of those associated with myocardial necrosis, in that they showed the predominant contribution of components 4 and 5.

Figure 9 is presented by way of contrast; it shows the distortion of the normal plasma pattern in a patient with homologous serum hepatitis. There is a distinct increase of component 1, in which normal human liver tissue is especially rich.

The enzymes we are interested in clinically, do not represent homogeneous single enzyme activities, but rather the sum of the component iso-enzymes. Therefore, we must re-evaluate the usefulness and the limitations of the methods employed clinically, and re-assess all of the enzyme techniques (those that have been discarded as well as those that are in use). From this we can determine how much new clinical information we can gather on the basis of this added insight into the composition of enzyme activities.

DR. TICKTIN: Dr. Wacker would you care to comment on Dr. Wróblewski's observations?

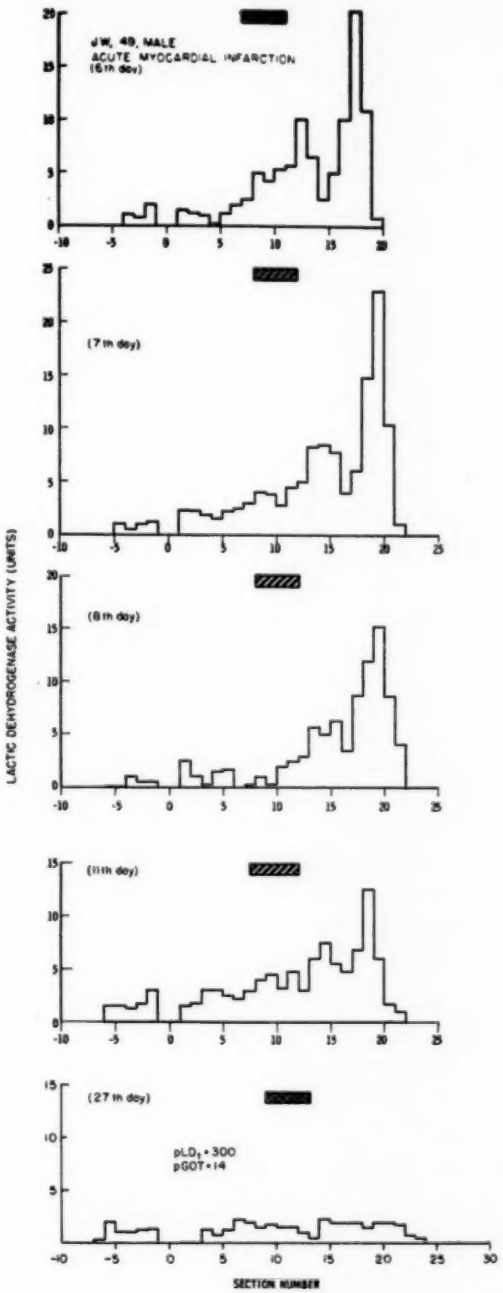

FIGURE 8

DR. WACKER: I would like to congratulate Dr. Wróblewski on this fine and interesting work. It will prove extremely fruitful diagnostically in providing some understanding of the changes in serum enzymes.

DR. TICKTIN: Dr. Wróblewski, would you care to comment on *the practical aspect of the use of iso-enzyme determinations, since the method (starch-block electrophoresis) is fairly complicated.*

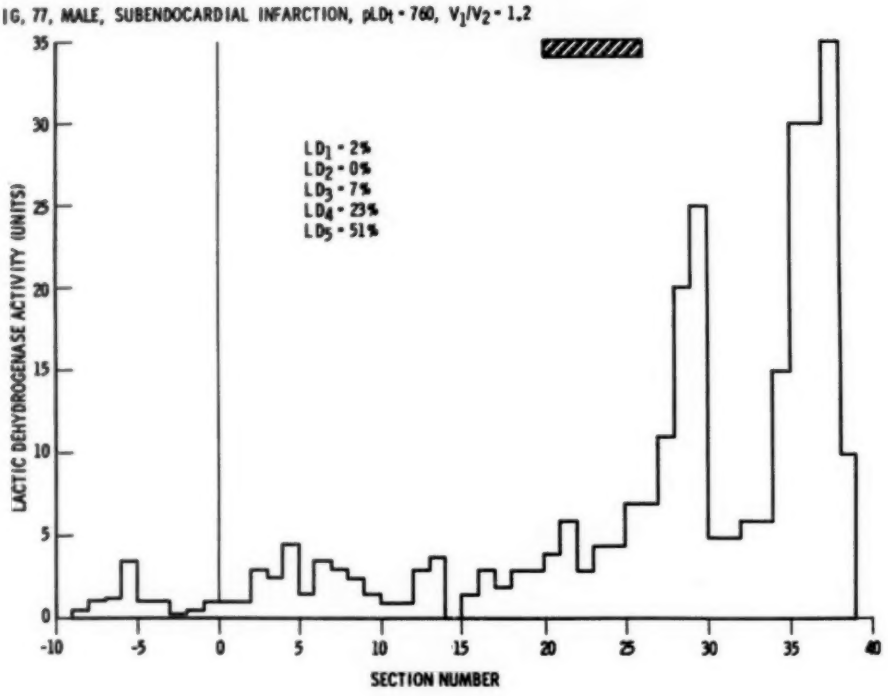

FIGURE 9

DR. WRÓBLEWSKI: The methods that I have described are somewhat tedious and time-consuming. However, they are not beyond the capabilities of any general laboratory. They require some experience, but this is true of all methods. First, we have to establish their reliability and usefulness. Then, if the information gained from these approaches is particularly outstanding and not available by present methods, someone with imagination and originality will come up with a simplified method.

DR. TICKTIN: Dr. Wacker, *do your observations on serum LDH elevation in pulmonary infarction apply also to pulmonary embolism without infarction?*

DR. WACKER: Yes, but the only basis for an absolute diagnosis of pulmonary embolism is postmortem proof. We have had about 3 cases of pulmonary embolism without any evidence of infarction. In these 3 instances, the serum LDH pattern was virtually the same as in cases with infarction. Although the data are meager, apparently the serum LDH level rises in pulmonary embolism without infarction.

DR. TICKTIN: Dr. Wróblewski, *using total SGOT, SGPT and LDH levels (not iso-enzyme patterns), can myocardial disease be differentiated from hepatic disease?*

DR. WRÓBLEWSKI: More often than not, but the same thing could be said about the clinical findings in the absence of these tests. One can usually diagnose coronary occlusion and myocardial infarction by the history alone. Enzyme tests, however, do increase the reliability of the clinical conclusion. I would not like to leave the impression that even these three enzyme tests together should be used as the only basis for drawing final conclusions. Perhaps I'm belaboring this

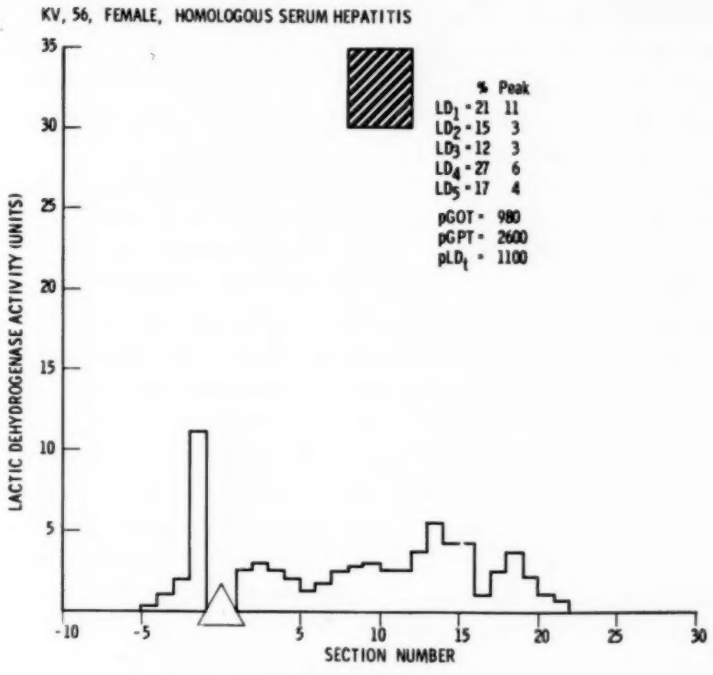

FIGURE 10

point, but it is very important. I have seen several cases in which serious clinical errors of judgment have been predicated on too great confidence in plasma enzyme measurements.

DR. TICKTIN: Dr. Wacker, *is the SGOT level elevated as long as the pain of myocardial infarction persists?*

DR. WACKER: I don't know. You could probably answer that question better than I.

DR. TICKTIN: Dr. Wróblewski?

DR. WRÓBLEWSKI: There is no relationship between the pain and the elevation of enzyme activity. There may be no relationship between the pain and myocardial infarction. Certainly there is no relationship between persistence or lack of pain and changes in plasma enzymes.

DR. TICKTIN: Dr. Wróblewski, *what direct evidence is there that the increased levels of serum enzymes are due to liberation of enzymes from damaged tissue? Have these enzymes ever been injected into animals and shown to remain in the blood for several days as they do in patients after myocardial infarction?*

DR. WRÓBLEWSKI: When purified crystalline enzyme, or aqueous extracts of tissue from the same species, are injected into experimental animals, the degradation of these enzymes is much more rapid than that observed in patients. In the animal, the enzyme is usually administered as one dose or as an infusion. In addition, the homeostatic mechanism in an intact animal without myocardial infarction is quite different from the distorted homeostatic mechanisms at play in the cardiac patient. Therefore, one should not necessarily relate the observations in animals with those in man.

There is strong evidence, based on clinical experience and on the assay of human tissues, that in diseases other than myocardial infarction, the elevation of plasma enzyme levels and the alteration in their patterns and rates of degradation are related not so much to the release of these enzymes from within the cell, but to an elaboration of these enzymes by tissues and cells.

DR. TICKTIN: *Are the enzymes cleared through renal mechanisms, that is, filtered and/or excreted?*

DR. WRÓBLEWSKI: Often they are not. Homeostatic mechanisms other than the kidney play a role. Even enzymes like amylase (which appears in the urine in sizable amounts) are removed or handled homeostatically by organs other than the kidney. From present information, many other enzymes, such as transaminase and lactic dehydrogenase, are not handled through the kidneys. For example, in animal experiments one can remove both kidneys and cause myocardial infarction, yet the serial changes in serum enzyme levels will be the same as in an animal with intact kidneys. This is also true in certain clinical situations—for example, in cases of renal shutdown with superimposed myocardial or pulmonary infarction; here the kidney plays only a slight role, if any, in the homeostatic mechanisms concerned with the changes in plasma enzymes.

What factors do play a role? Possibly the biliary tract, or even the liver itself, which controls proteins. After all, enzyme activities are primarily an expression of changes in globulin. Since the liver and some other organs can handle proteins so effectively, more likely these organs rather than the kidney are important factors in controlling plasma enzymes.

DR. TICKTIN: One last question for Dr. Wacker. Would you comment on *the accuracy of these enzyme determinations?*

DR. WACKER: That depends upon the standard of accuracy. I can obtain fairly accurate results with the LDH test in cases of myocardial infarction, and Dr. Ticktin has obtained almost 100 per cent accuracy with the SGOT test. Without doubt, there is a rise in the level of serum enzyme activity in association with myocardial infarction. The precision of the method, *i.e.*, the reproducibility of the results under the same circumstances and using the same instruments, is about 5 per cent.

DR. WRÓBLEWSKI: Dr. Wacker, *are those "circumstances" the same whether in Washington or Boston?*

DR. WACKER: Yes. Using the simplest instrument that has yet been devised for measuring optical density changes at 340 millimicrons, the precision is about 6 per cent.

DR. WRÓBLEWSKI: In our laboratory, it is closer to 15 per cent.

DR. TICKTIN: In our original study we used the Beckman DU spectrophotometer; duplicate samples were also processed on a Spectronic 20. The difference in results between the two instruments was about 6 per cent.

DR. WACKER: The LDH assay in the forward direction is more precise than the SGOT and SGPT assays. That is why we prefer the LDH tests.

DR. TICKTIN: Our time has run out. Both of our panelists have been most articulate and have presented their points very well. It is worth mentioning again that we have covered only one small aspect of clinical enzymology.

INTRODUCTORY REMARKS—AFTERNOON SESSION

JOHN B. JOHNSON, M.D.*

Washington, D. C.

The District of Columbia General Hospital considers it one of its responsibilities to participate in the continuing postgraduate work of physicians, particularly private practitioners. For this reason it has joined with the District of Columbia Branch of the American Women's Medical Association, and the Maryland Academy of General Practice in sponsoring this symposium. Our respects go also to the Hoffmann-La Roche company for financial assistance in this program.

The science of genetics, born about one hundred years ago with the work of the Austrian abbot, Gregor Mendel, has grown rapidly by means of a vast number of contributions, including some on human genetics. However, it was not until four or five years ago that the genetic factors in disease became important in clinical practice; today many medical schools offer courses in medical genetics.

Four major achievements have made possible these phenomenal changes during the past years: 1) the perfection of human tissue culture, 2) the arrest of mitosis in cultures, before spindle formation, 3) the use of hypertonic solutions to disperse chromosomes, and 4) the squash technique for studying chromosomes. These new advances have greatly facilitated the study of chromosomes.

Our first speaker today, Dr. Victor McKusick, is one of the few men whose interest in the genetic and hereditary aspects of medicine can be said to have started at birth. He is one of identical twins, and his interest in genetics has been with him through high school, college and medical school because he can't get rid of his heredity.

Dr. McKusick first became interested in the medical aspects of genetics when, together with Jaegers, he studied the hereditary nature of polyposis of the colon associated with pigmented spots in the intestinal tract. In 1949 he became interested in Marfan's syndrome, and since that time has carried out some interesting research on this condition. At present, Dr. McKusick is Professor of Medicine and Director of the Division of Medical Genetics in the Department of Medicine at Johns Hopkins University, Baltimore, Maryland.

Our second speaker, Dr. John La Due, has had an enviable career in medicine. He is one of the few internists in America to hold the degrees of Master of Science and Doctor of Philosophy in general medicine. He performed a great deal of original work on digitalis, and on the fibrinolysins and their relationship to the dissolution of clots and various types of thromboses, including coronary thrombosis. More recently he has been trying to develop a more sensitive, and at the same time safer, method for the early detection of coronary insufficiency. At present he is Associate Professor of Clinical Medicine at Cornell Medical College and head of the section in cardiology at the Sloan-Kettering Institute, New York.

* Professor of Medicine, Howard University.

The final portion of the afternoon session will be devoted to a discussion on the management of arrhythmia. Any physician who has dealt with adult patients is aware of the fact that frequently a patient recovers from serious failure of cardiac muscle, only to die from failure of cardiac rhythm. This problem of cardiac arrhythmia is very important and extremely difficult to treat. We are privileged today to have a panel of experts discuss the various methods for handling this problem. The moderator for this section of the program is Dr. John Evans.

Dr. Evans has carried on considerable work in this field. He is Associate Professor of Medicine at George Washington University Medical School, Washington, D. C., and Director of the Cardiac Clinic and Heart Station at George Washington University Hospital where he also directs a graduate training program in cardiology. Dr. Evans will introduce his Panel.

GENETIC FACTORS IN CARDIOVASCULAR DISEASES*

VICTOR A. McKUSICK, M.D.†

Baltimore, Maryland

In a discussion of the role of hereditary factors in the four major types of cardiovascular disease, *i.e.*, atherosclerosis (including coronary artery disease), hypertension, rheumatic heart disease and congenital malformations of the cardiovascular system, it is important to keep in mind the multifactorial nature of causation in these conditions. When singling out a genetic factor in cardiovascular disease, one must not underrate the importance of non-genetic factors. In coronary arterial disease, for instance, it cannot be said that heredity, any more than diet, stress or physical inactivity, is *the* cause. Similarly in rheumatic fever, the possibility of a genetic factor in susceptibility does not deny the paramount importance of the streptococcus. It must be stressed that the major cardiovascular diseases result from a combination of factors, of which heredity is but one.

With this in mind, we shall discuss first some of the statistical and genetic evidence bearing on the major forms of cardiovascular disease, and then some of the rarer conditions in which genetic factors appear to be even more directly involved.

ATHEROSCLEROSIS

In atherosclerosis it may be useful to think of the etiology as involving a multiplicity of factors converging on the central problem. Some of the factors are largely environmental and some are hereditary (Fig. 1); and though there may be dispute as to the role played by some of these components, the principle of collaborating factors must be emphasized.

In coronary artery disease, in particular, there seems to be reasonably good evidence to support the clinical impression that there is familial aggregation. The concentration of cases in families cannot be fully explained by environmental factors; thus, by exclusion, the cause is considered to be in part genetic (1–4). However, much more work is necessary along this line, since the evidence leaves much to be desired.

Once a genetic factor has been established for a given disease, especially one of these common conditions, the mechanism by which the gene produces increased susceptibility must be determined. In the case of coronary artery disease there are at least 3 possible mechanisms:

1. There is strong evidence that lipid metabolism (including more flagrant forms of deranged metabolism (Fig. 2) and the milder degrees of hypercholesteremia) is under genetic control (5–7). The distribution of disorders of

* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D.C., November 3, 1960.

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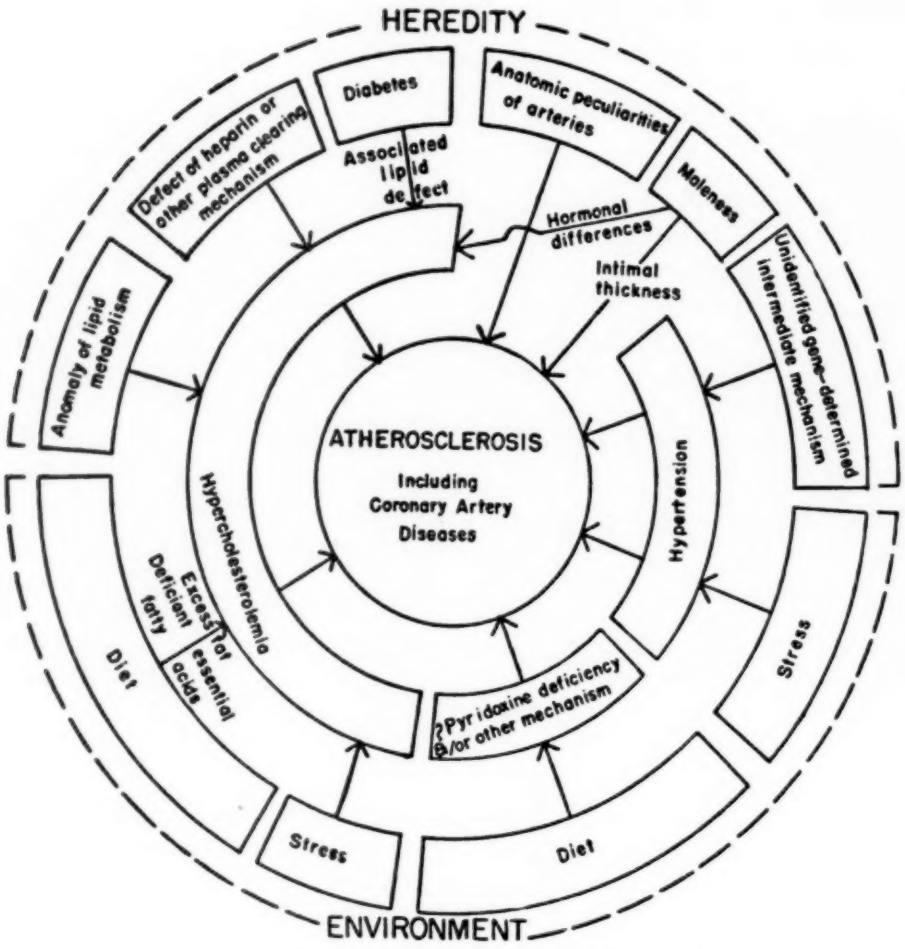

FIG. 1. The multifactorial causation of atherosclerosis. (Courtesy of the Eugenics Quarterly.)

lipid metabolism within families follows a pattern that would be inexplicable in terms of environmental factors alone.

2. There may be individual, genetically determined differences in coronary anatomy (8). In man, three patterns of major branching of the coronary arteries have been identified (9): *a*) left artery preponderance, *b*) right artery preponderance, and *c*) a balanced artery pattern. It is claimed, with considerable justification, that the frequency of myocardial infarction (coming to the attention of the pathologist) is different for the three basic patterns, being least in the balanced pattern. Direct evidence that the pattern of coronary anatomy is genetically determined is obviously difficult to obtain, but some inferences may be drawn from information regarding other vascular areas, *e.g.*, the branching of the aorta and the venous patterns of the anticubital fossa.

3. Temperament and personality, at least in part, are genetic factors. Even the newborn infant has personality characteristics which can scarcely be environ-

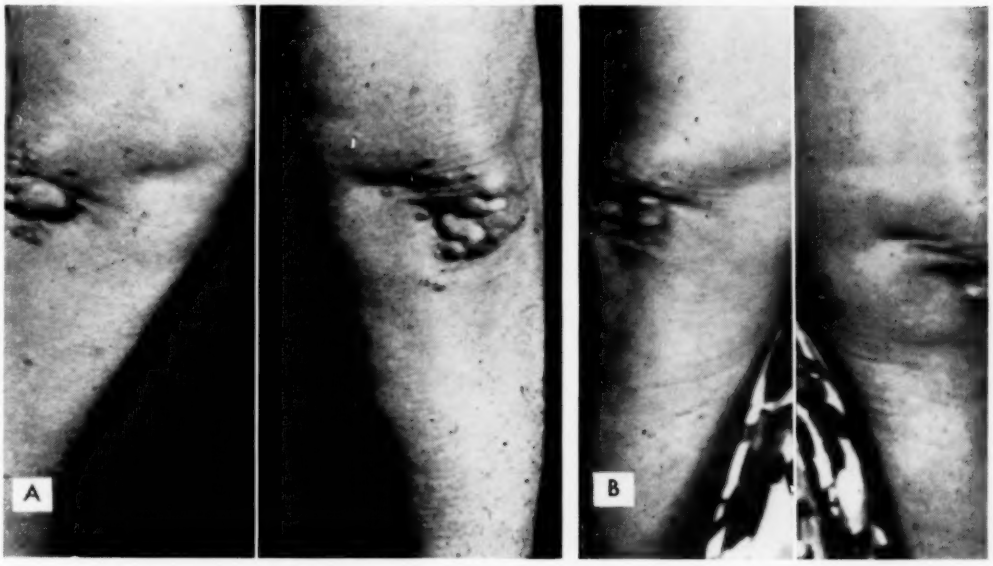

FIG. 2. *Hereditary hypercholesterolemia with xanthomatosis and angina pectoris.* Lesions of elbows of patient: (**A**) before, and (**B**) after regimen to reduce weight and serum cholesterol level. The angina pectoris was relieved. (Courtesy of Dr. F. R. Franke, Pittsburgh, Pennsylvania.)

mentally determined at that stage. The exact relationship between the personality pattern and the pathogenesis of coronary heart disease is vague at present, but has received increasing attention in recent years.

HYPERTENSION

There is a somewhat heated controversy in England concerning the heredity of hypertension. Although there is agreement among these English workers that genetic factors are important, the question remains whether essential hypertension is a separate entity determined by a single gene in a straightforward Mendelian manner, or whether it is merely the upper end of a so-called continuous distribution determined by multiple genes.

This can be made clearer by an analogy to body stature. Height is not determined by a single gene, but by a constellation of genes. If they add up to one's being 6 feet 6 inches tall, then that will be the height. In the view of Sir George Pickering and his school (10–12), blood pressure is a similar trait; the level of blood pressure is determined by multiple genes in collaboration with environmental factors. Furthermore, there is evidence of correlation between the blood pressure of a given person and that of his relatives (13–15). Thus if the blood pressure level is high in the person chosen as the index case (propositus), the average blood pressure in the relatives will also be high (Fig. 3).

There is also a form of hypertension, pheochromocytoma, in which the genetic factors can be established in a certain proportion of the cases (16). Pheochromocytoma occurs rather frequently in association with von Recklinghausen's

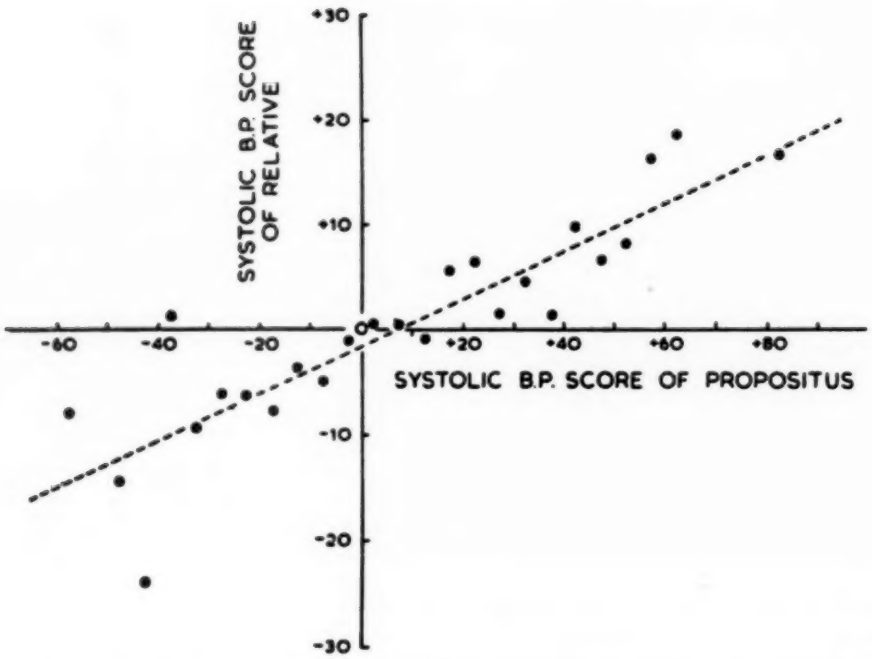

FIG. 3. The relationship between systolic blood pressure (expressed as a score) in index cases (propositi) and the mean systolic scores in first degree relatives. [From Miall and Oldham (14).]

neurofibromatosis (Fig. 4), which is inherited as an autosomal dominant. In fact, pheochromocytoma was found to be associated with neurofibromatosis in 5 per cent of the recorded cases (4, 17). It is possible that the true frequency of this association is even higher, since it is easy to pass over the minor manifestations of neurofibromatosis such as cutaneous tumors or "café au lait" spots on the skin.

RHEUMATIC HEART DISEASE

Susceptibility to rheumatic fever may be genetically determined to a significant degree. The results of large studies conducted in major cities of the United States (18–19), Canada (20) and Europe (21) indicate that the disease is concentrated in families, but such studies are unsatisfactory evidence for genetic predisposition. On the other hand, the frequency of rheumatic fever in sibs according to whether neither, one, or both parents were rheumatic, supports the genetic theory. Definite statements must await further study.

CONGENITAL MALFORMATIONS

The physician is often asked by parents: "We have had a child with congenital heart disease. What is the risk that another child will be similarly afflicted?" For the more common forms of congenital heart disease such as ventricular septal defect, coaretation, patent ductus arteriosus or atrial septal defect, there are some empiric figures regarding this risk; these can serve as a basis for an answer.

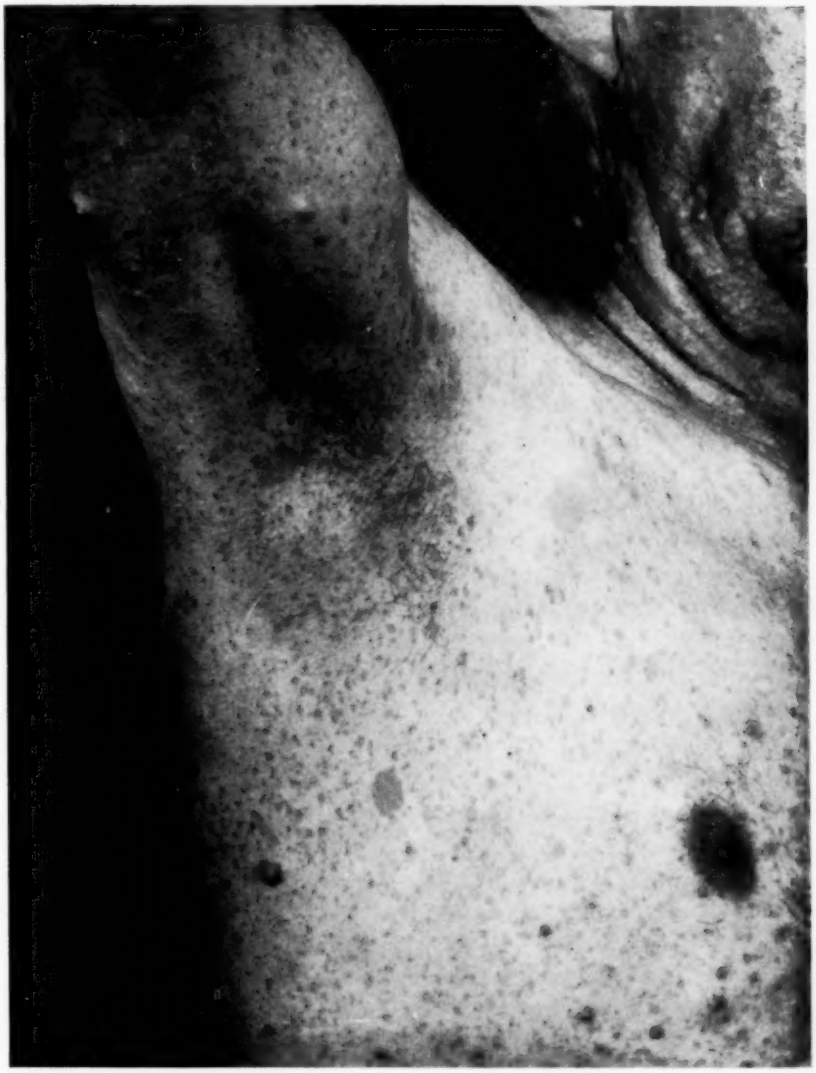

FIG. 4. *Pheochromocytoma in association with neurofibromatosis.* Note the café-au-lait spots and tumors of the skin in a patient from whom a pheochromocytoma was removed in 1950.

The frequency of congenital heart disease among sibs has been determined in a few studies; it is in the order of 2 per cent. Although this is a risk that may not impress parents as excessive, it should be viewed with caution, since one occasionally observes families that have a most astounding frequency of congenital heart defects.

Another question which is being asked of physicians by an increasing number of patients is: "I have had congenital heart disease and have been operated on successfully. What is the risk of my future children being similarly affected?" The statistical figures on this subject are far from complete. However, it appears that the frequency will be of the order of 2 per cent or somewhat higher.

SPECIAL FORMS OF CONGENITAL HEART DISEASE

Some forms of congenital heart disease are inherited in a fairly direct Mendelian manner. For example, endocardial fibro-elastosis appears to be inherited as a simple autosomal recessive trait (22). It can occur in several siblings from normal parents (Fig. 5), and the proportions in which it occurs seem to be appropriate for a recessive trait.

Another interesting, although rare, disorder is the Ellis-van Creveld syndrome. In this disease there may be polydactylism, chondrodystrophy with short extremities, and dystrophy of the nails; the most frequent cardiac malformation is a triloculate heart with one atrium (23). It is inherited as an autosomal recessive (24), occurring only once in every 4 million persons (25).

Hereditary methemoglobinemia produces cyanosis, simulating cyanotic congenital heart disease, but does not involve any malformation of the cardiovascular system (26). This condition occurs in two forms, one of which is easily corrected by sustained supplementation with vitamin C.

One of the most significant and important findings in current basic medical research is the demonstration of chromosomal aberrations in congenital disorders. One of the conditions in which chromosomal aberrations have been demonstrated is mongoloid idiocy. The fundamental error in mongolism is the presence of an extra autosomal chromosome due to "non-disjunction" of one pair of chromosomes during maternal gametogenesis, resulting in 47 instead of the normal 46 chromosomes (27–28). Cardiologic interest in mongolism stems from the fact that about 37 per cent of these patients also have a cardiac malformation (29). The lesions are rather characteristic, being usually an atrioventricular cushion defect, such as the ostium primum type of atrial septal defect.

Chromosomal aberration is also demonstrated in Turner's syndrome. This is phenotypically a female condition, in which the subjects have only 45 chromosomes, the absence of one of the X chromosomes giving rise to the so-called XO sex chromosome constitution (30). These patients are of short stature, with webbed necks, hypoplastic mandibles, low-set ears, underdeveloped breasts, and infantile internal genitalia; coarctation of the aorta is frequently present, as well as hypertension (31, 32).

RARE DISORDERS OF PRIMARILY GENETIC ETIOLOGY

There are a few less common conditions in which there is extensive heart involvement (Table 1). Although individually rare, in the aggregate these disorders form a significant group. In a previously published survey (33, 34), we discussed in detail both the common disorders mentioned earlier and these less common conditions; therefore we shall limit our discussion to the Marfan syndrome.

The mode of inheritance in this syndrome appears to be that of a Mendelian dominant, but cases frequently occur that are apparently sporadic, and perhaps mutant. The victim of the disease (Fig. 6) is likely to show abnormality in one or all of three of these areas: 1) the eye—dislocation of the lens; 2) the skeletal system—excessive length of the extremities, loose joints, spinal curvature, malformation of the rib cage and sternum; and 3) the cardiovascular system—

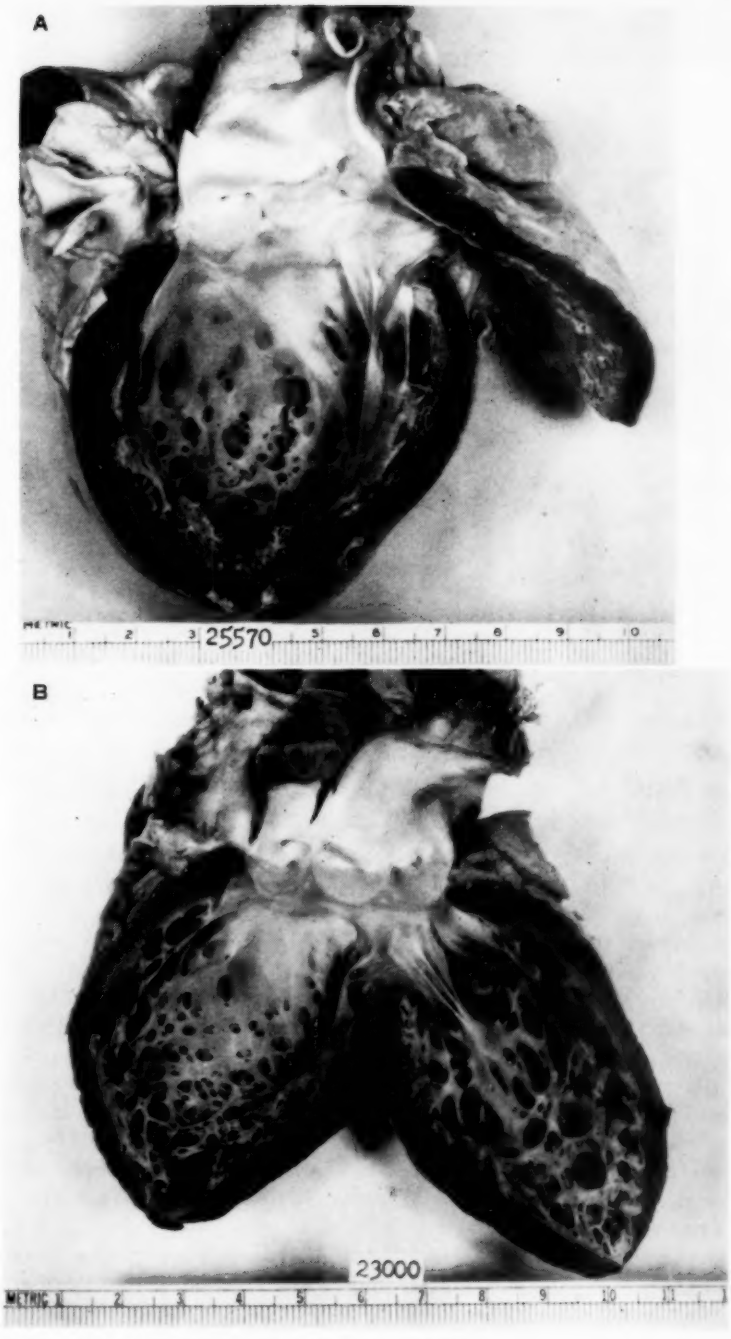

FIG. 5. *Endocardial fibro-elastosis in brother and sister.*

Upper photograph: Heart of *G. S.* (A83748; aut. 23000), colored female, born in June 1950, first admitted in March 1951, died in April 1951 because of heart failure. Autopsy revealed extensive endocardial fibro-elastosis of the left ventricle with mural thrombus formation.

Lower photograph: Heart of *W. S.* (B6967; aut. 25570), brother of G. S., born in December 1951, and died in February 1955. He was the product of his mother's eighth pregnancy. In addition to Patient G. S., there were 4 living normal children and there had been 2 miscarriages. Both parents were normal. Patient W. S. had several admissions because of heart failure. Surprisingly, the same diagnostic confusion obtained as in the case of the sister, largely because no effort was made to obtain information regarding the cause of death in the sib. Autopsy showed endocardial fibro-elastosis and the changes of chronic heart failure.

TABLE 1

Less Common Genetic Disorders With Significant Cardiovascular Implications

Neuromuscular Syndromes:
- Myotonic dystrophy
- Pseudohypertrophic progressive muscular dystrophy
- Friedreich's ataxia
- Familial periodic paralysis
- Tuberous sclerosis
- Riley's dysautonomia
- Neurocirculatory asthenia

Heritable Disorders of Connective Tissue:
- Marfan syndrome
- Pseudoxanthoma elasticum
- Hurler syndrome
- Ehlers-Danlos syndrome

Some Myocardial Disorders:
- Glycogen storage disease
- Familial cardiomegaly
- Hemochromatosis
- Primary systemic amyloidosis

Conduction Defects, Arrhythmias and ECG Variants

Some Disorders of Blood Vessels:
- Osler-Rendu-Weber's multiple telangiectasia
- Milroy's disease
- Werner syndrome
- Intracranial "berry" aneurysm

Miscellaneous Other Disorders

weakness of the media of the aorta. This defect in the aorta may lead to dissecting aneurysm, diffuse aneurysm, or a combination of the two. Sometimes in persons genuinely afflicted with this condition, some of these characteristics may be lacking, but the reason for this is not known.

The following case history will serve to present the cardiovascular aspects of the syndrome:

A 37-year-old man came to the Johns Hopkins Hospital because of symptoms produced by aortic regurgitation. There was no evidence of the usual causes for this valvular lesion. However, he informed us that he was employed as a riveter and that the instrument would sometimes slip and hit the front of his chest forcefully. Thus it was thought possible that he had traumatic aortic regurgitation.

When he was seen one year later there was obvious aggravation of the earlier symptoms, with marked dilatation of the first part of the ascending aorta. It was also noted that he had iridodonesis. (This billowing of the iris appears to be caused by dislocation of the lens with loss of the usual support behind the iris.) Careful ophthalmologic examinations were carried out, which confirmed the ectopia lentis. It was now clear that this was a case of the Marfan syndrome.

At autopsy there was a diffusely dilated ascending aorta with tremendous stretching and sacculation of the aortic cups and hypertrophy of the ventricles. Histologic examination of the aorta showed loss of elastic fibers and the development of lacunae containing metachromatically staining material.

A point of some clinical importance is that in most cases of this syndrome the first part of the aorta to undergo progressive dilatation is the base in the vicinity of the sinuses of Valsalva. This is deep within the silhouette of the heart, so that an impressive degree of aortic regurgitation may be present before there is any x-ray evidence of aortic dilatation. A few years ago we surveyed all the cases of ectopia lentis at the Wilmer Eye Institute and found that approximately 70 per cent of these patients could be considered to have the Marfan syndrome. Among the patients were several who had aortic regurgitation, but no abnormality by x-ray examination.

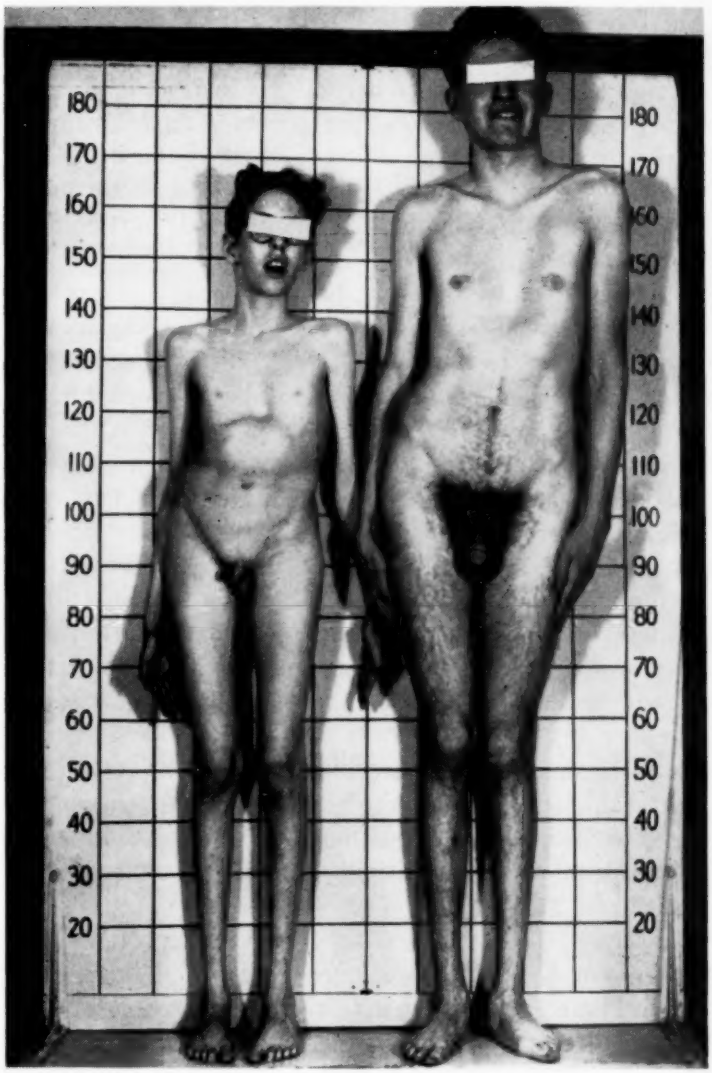

FIG. 6. *The Marfan syndrome in two brothers.* The father of these brothers had a chest deformity and aortic regurgitation; he died at the age of 35 years. The younger brother has severe scoliosis, ectopia lentis and pectus excavatum, but there is no evidence as yet of cardiac abnormality. The elder brother, who has only skeletal deformity, undoubtedly has the Marfan syndrome, *i.e.*, carries the gene with incomplete expression. Note that if it were not for the family history of indubitable cases, one could not be certain of the diagnosis in the older brother.

We followed a number of these cases for a period of years. In almost all instances the ascending aorta was predominantly affected, but there were rare exceptions. One 26-year-old man with a depressed sternum and some asymmetrical deformity of the chest, presented with a pulsatile mass in the abdomen. This was due to a diffuse change in the abdominal aorta which, in this case, began just above the diaphragm and extended down to the iliac arteries.

The youngest patient in the series with the Marfan syndrome was a stillborn child, but the youngest patient studied in clinical detail was a 26-month-old boy.

Even when the boy was first seen, the disease was extremely severe. There was "wide-open" aortic regurgitation, grossly dislocated lenses, striking skeletal abnormalities, and a combination of hernia and hydrocele.

The spectrum of severity in this condition is very wide. It should be emphasized that pectus excavatum may occur and overshadow the other manifestations. This is not to say that all patients with pectus excavatum have the Marfan syndrome, but the possibility should be kept in mind, particularly if there is a diastolic murmur.

One of the better skeletal indices of this syndrome is the ratio of the upper body segment to the lower body segment, the former being measured from the top of the pubic symphysis to the crown, and the latter from the top of the pubic symphysis to the floor. Usually this ratio is considerably higher in normal persons than in those with the Marfan syndrome. However, this principle cannot be applied indiscriminantly. For example, analysis of data we have gathered over the past few years has shown that the average Negro has not only longer legs, but also a shorter upper segment than the average white person. Thus when confronted by a patient, especially a Negro, with an increased arm span and excessive length of the extremities, even with aortic regurgitation and gangling habitus, the evidence is not sufficient for a diagnosis of the Marfan syndrome. There must also be careful ophthalmologic examinations and a look into the family history. Even then, if the results are negative, the diagnosis cannot be definitely established.

On the basis of the data we have gathered it has been possible to obtain some normal standards for both the white and Negro population (taking into consideration sex and age) with which the measurements of the individual patient can be compared. Although this is not a pathognomonic test, it is a step forward in diagnostic procedures.

Attempts were made to use the level of serum mucoproteins and the urinary excretion of hydroxyproline as diagnostic procedures in determining the presence of the Marfan syndrome. However, in investigations of serum mucoprotein levels, no difference could be established between persons known to have the disease and the controls which were matched for race, sex and age. The value of the urinary hydroxyproline excretion test for diagnostic purposes still requires confirmation.

CONCLUSION

An analysis of the genetic factors in cardiovascular disease is of importance because it potentially permits the recognition of susceptible individuals, thus allowing for more efficient administration of preventive and therapeutic management. Also, it is hoped that, through increased knowledge of the hereditary mechanism, will come methods for breaking the chain leading to cardiovascular disease.

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THE DYNAMIC EXERCISE ELECTROCARDIOGRAM*

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INTRODUCTION

Since our previous report, more than 300 electrocardiograms have been obtained on patients performing vigorous exercise (1). The purpose of this communication is to describe the method in detail, indicate the trend of normal variations, and discuss some of the findings in patients with abnormalities of the cardiovascular system.

Prior efforts at recording electrocardiograms during exercise have been only partially successful, since the resultant tracings have contained artifacts inherent in the system used (2–4). The two major difficulties that have been overcome in recording the electrocardiogram *during* exercise are skeletal muscle potentials and baseline shifts (Fig. 1). Skeletal muscle artifacts have been eliminated by attaching the electrodes to areas of the body which are virtually free of skeletal muscles; baseline shifts can be avoided by proper fixation of the electrodes to the skin. Because of the location of the electrodes, the technic is referred to as the Ear-Ensiform-Precordial (EEP) system.

TECHNIC

A. *Apparatus* (Fig. 2)

1. Ear-lobe electrode consisting of a square (2 x 2 cm.) of stainless-steel wire mesh connected to a plug jack.[1] (Fig. 2b.)
2. Chest electrodes consisting of a piece (1 cm. in diameter) of stainless-steel wire mesh within a rubber tube 1 cm. thick and 1 cm. in diameter connected to a plug jack. (Fig. 2c.)
3. Electrode compound.[2]
4. Foam rubber cushions, 2 x 3 x 5 cm. (Fig. 2a.)
5. Chest straps.

B. *The EEP method* (Fig. 3)

1. The electrode is secured to the right ear lobe by adhesive tape and a paper clip.
2. The chest electrodes are filled over the brim with electrode compound and placed over the ensiform process, over the fifth rib in the V-3 position, the sixth rib in the V-5 position, and the seventh rib in the V-7 position. Each cup electrode is held in place by a "Band-aid" tape and a foam rubber cushion. The foam rubber cushions are held in place over the electrodes by tightly wound elastic chest straps.
3. The cables for the patient are attached as follows: a) With a four-channel machine (Figs. 4, 5 and 6)—the right arm cable to the right ear electrode; the left arm cable to the ensiform electrode; the left leg cable to the V-7 electrode; precordial cables to V-3 and V-5 electrodes; ground cable to the right arm. b) With a single channel machine, the attachments are the same except that the left leg cable is attached to the V-5 electrode and the single precordial cable to the V-3 electrode.

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* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November, 3, 1960.

[1] RCA plug jack-phono input.

[2] Medcraft Electronic Corporation electrode paste (resistance 200 ohms), Catalog No. 773; Babylon, N.Y.

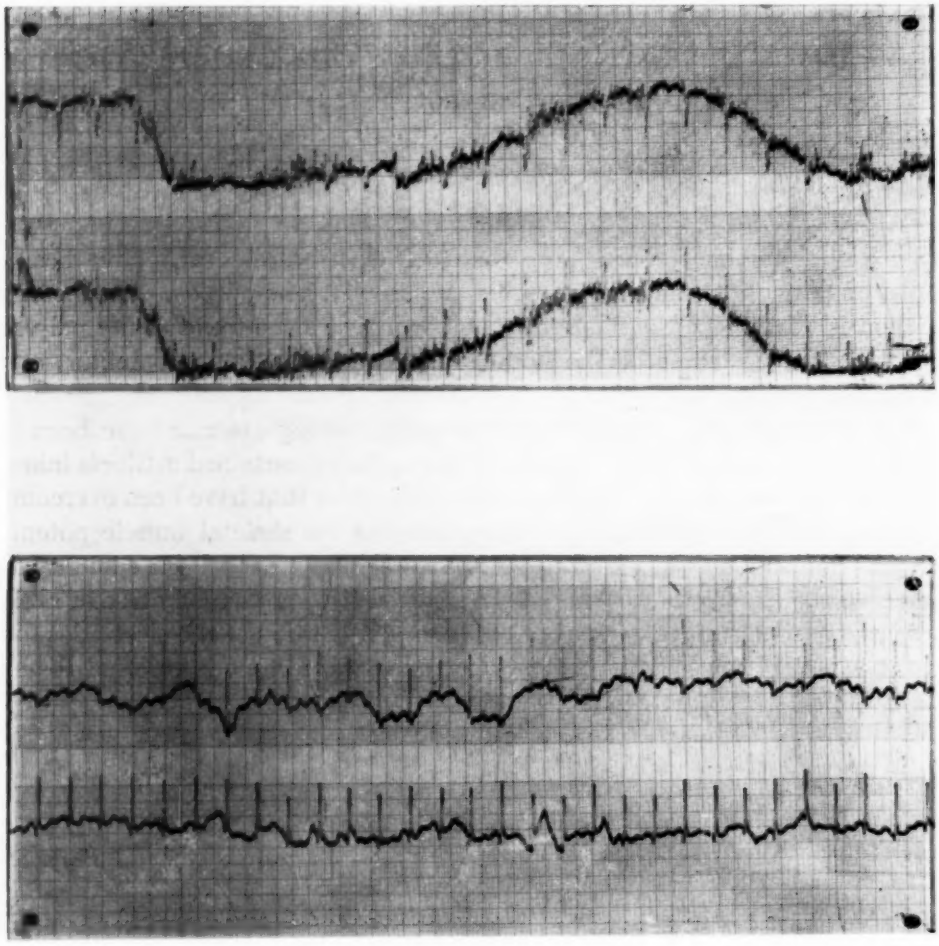


FIG. 1. Two problems involved in recording the electrocardiogram during muscular activity with the conventional lead system: (upper tracing) muscle artifacts and wandering base line, and (lower tracing) baseline shift.

4. The cables to the patient and the plug jacks are held in place by an Ace bandage.
5. The precordial leads Ve, V-3, V-5 and V-7 are recorded on channels AVL, V, V, and AVF respectively.
6. Patients perform the two-step exercise for three minutes.

C. *Special considerations*

In order to avoid muscle tremor and baseline shift during the actual performance of exercise, special attention should be given to the following points.

1. The skin should be free of hair and cleansed with alcohol.
2. The ensiform process should be located exactly, and the electrode carefully placed thereon. In the absence of the ensiform process the technical excellence of the tracings cannot be assured.
3. The other precordial electrodes should be fastened onto the ribs and not in the intercostal spaces.
4. The tip of the cable to the patient is cleaned with sandpaper and attached securely to the plug jack.

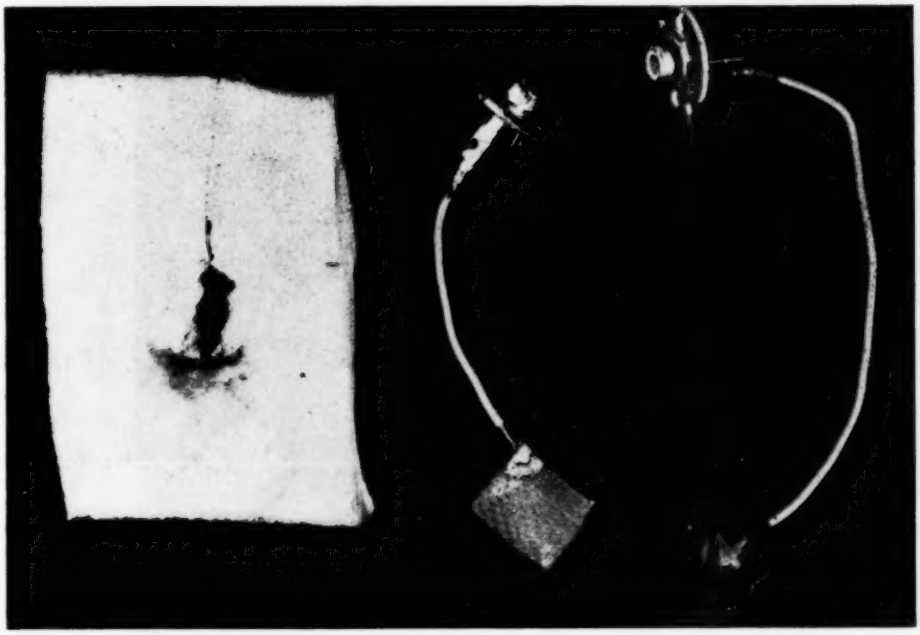


FIG. 2. Foam rubber cushion, wire mesh electrode for ear lobe, and precordial electrode

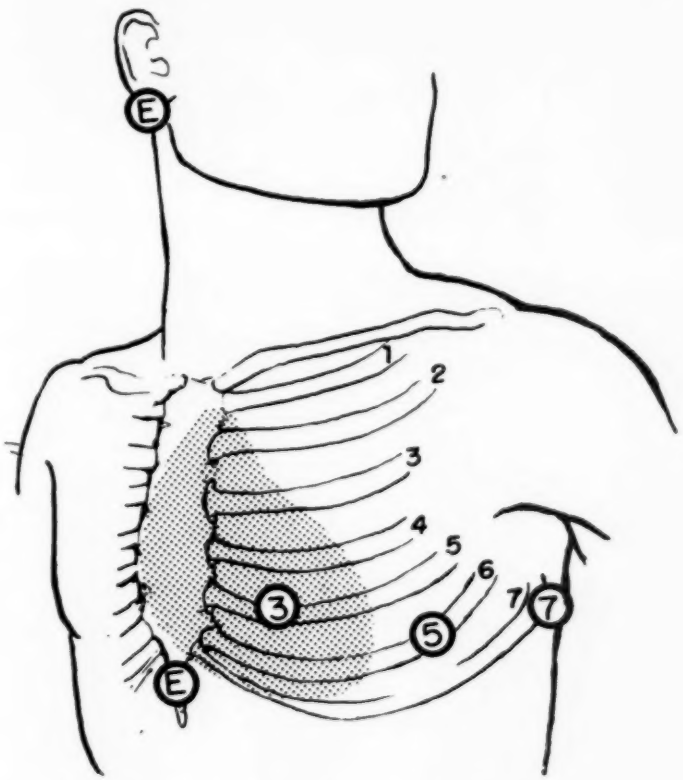
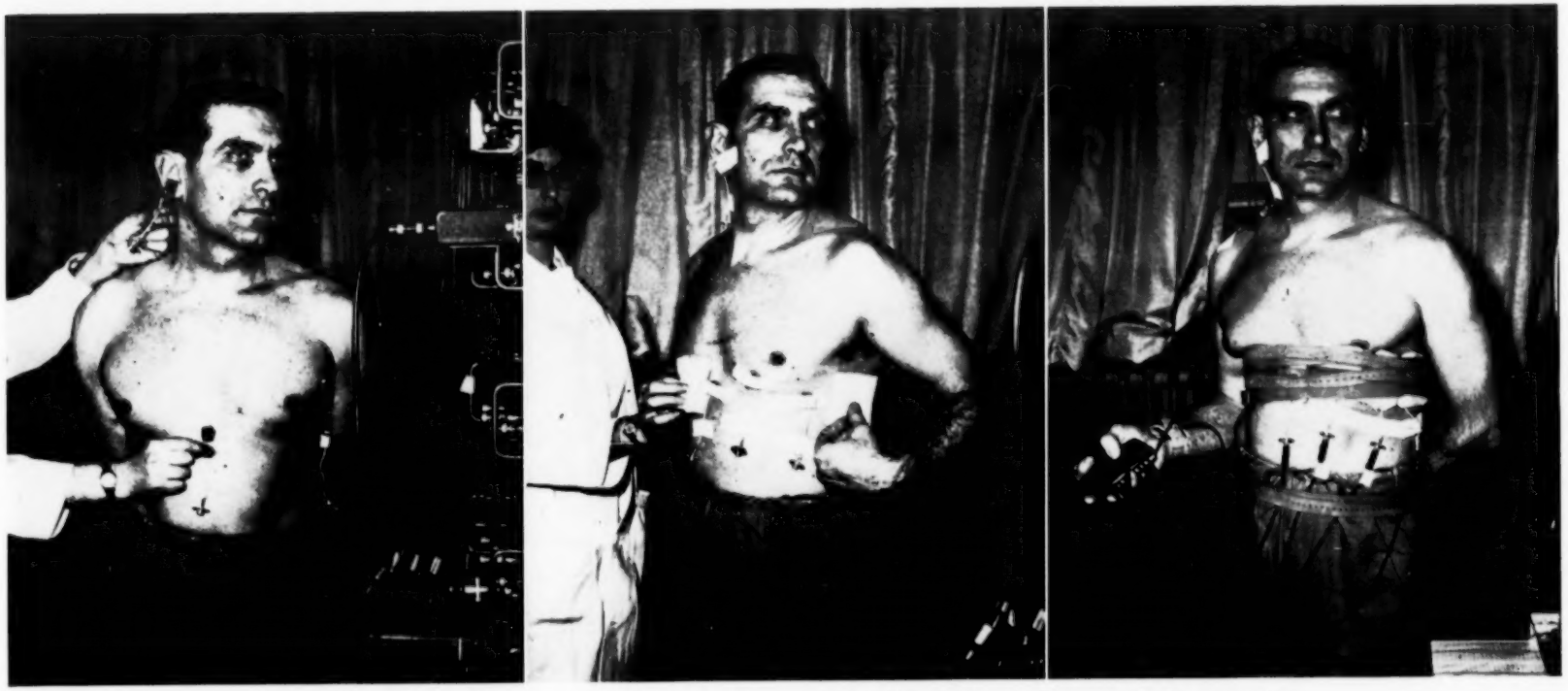


FIG. 3. Electrode positions in the EEP system.



FIGS. 4, 5 and 6. Placement of electrodes for recording the electrocardiogram during exercise.

5. To insure good conduction, fresh electrode paste is used for each test.

6. The over-all attachments should be checked and loose connections localized by tugging on each cable and tapping each electrode. The absence of baseline shift indicates proper electrode placements.

RESULTS

Of the more than 300 electrocardiograms recorded during exercise, 95 per cent were free of distortion (Fig. 1). In parts of all tracings, exact measurement of the amplitude and duration of all complexes was possible. Muscle activity such as is involved in running, jumping, hyperventilation or movements of the trunk, failed to distort or affect significantly the excellence of the tracings.

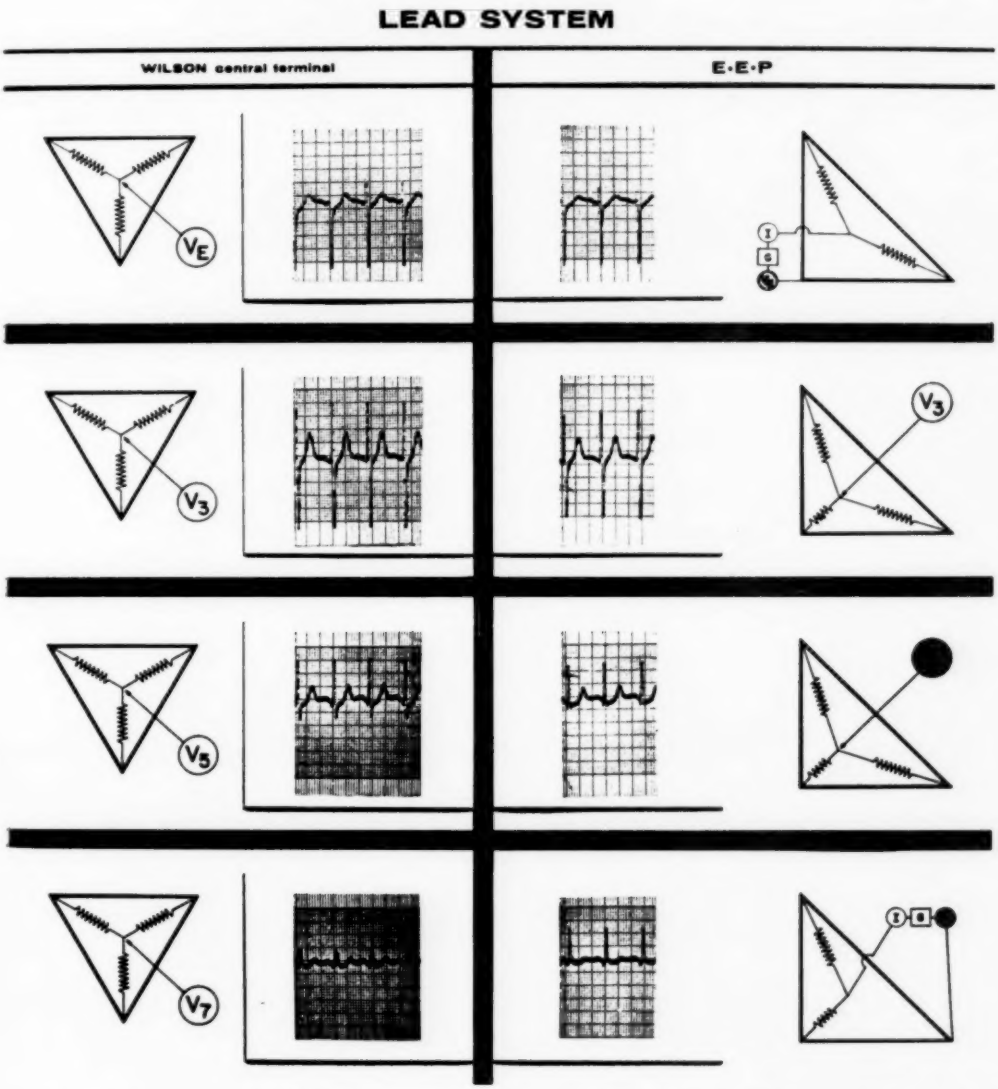


FIG. 7. Close resemblance of electrocardiograms taken with the Wilson central terminal and with the EEP system.

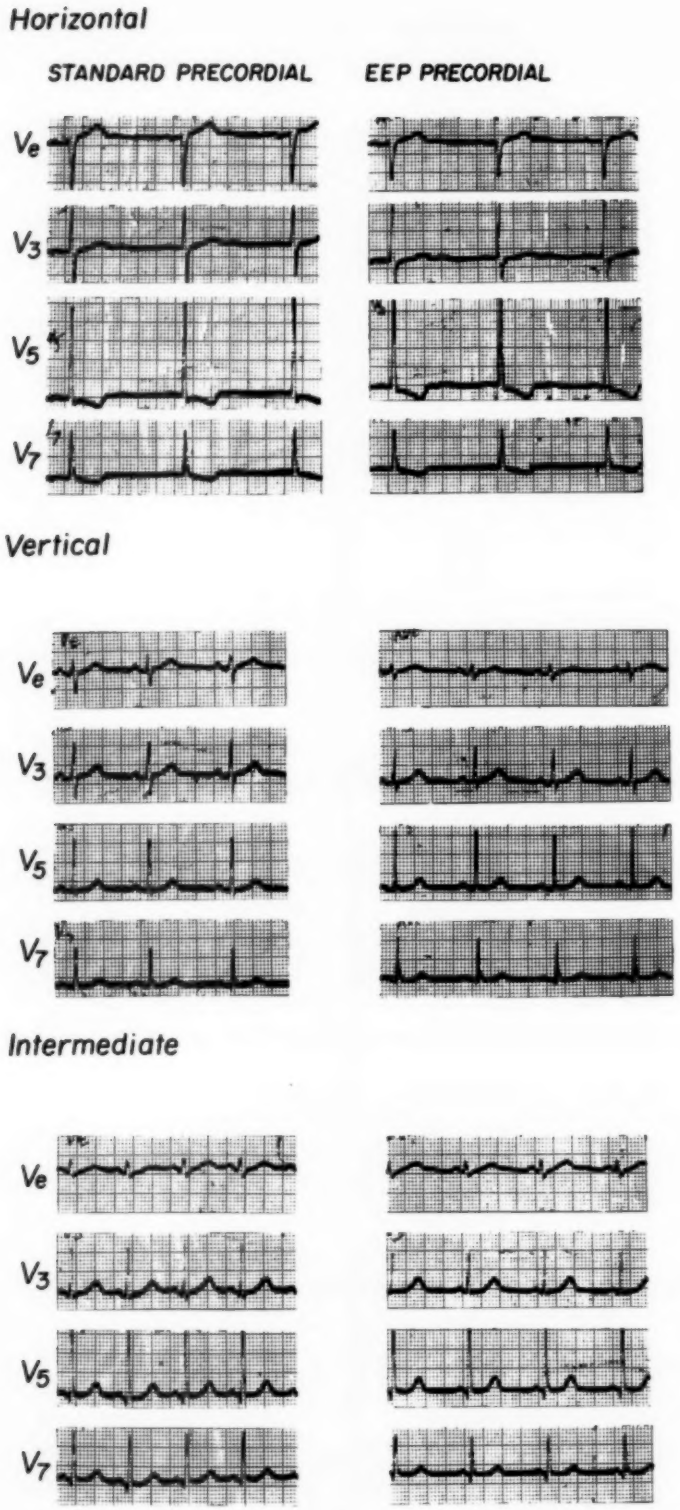


FIG. 8. Demonstration of how little the position of the heart (horizontal, vertical or intermediate) affects electrocardiograms obtained by either the conventional or the EEP system.

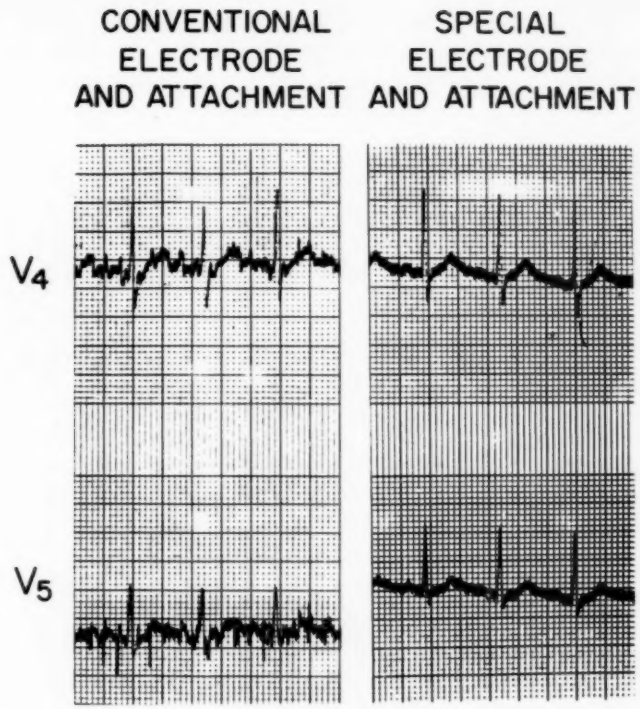


FIG. 9. Electrocardiograms obtained on a patient with parkinson-like tremor (left) and a patient with Parkinson's disease (right) during exercise. Note the presence of muscle artifacts in the conventional tracing, but the steady base line and lack of muscle artifacts in the EEP-system tracing.

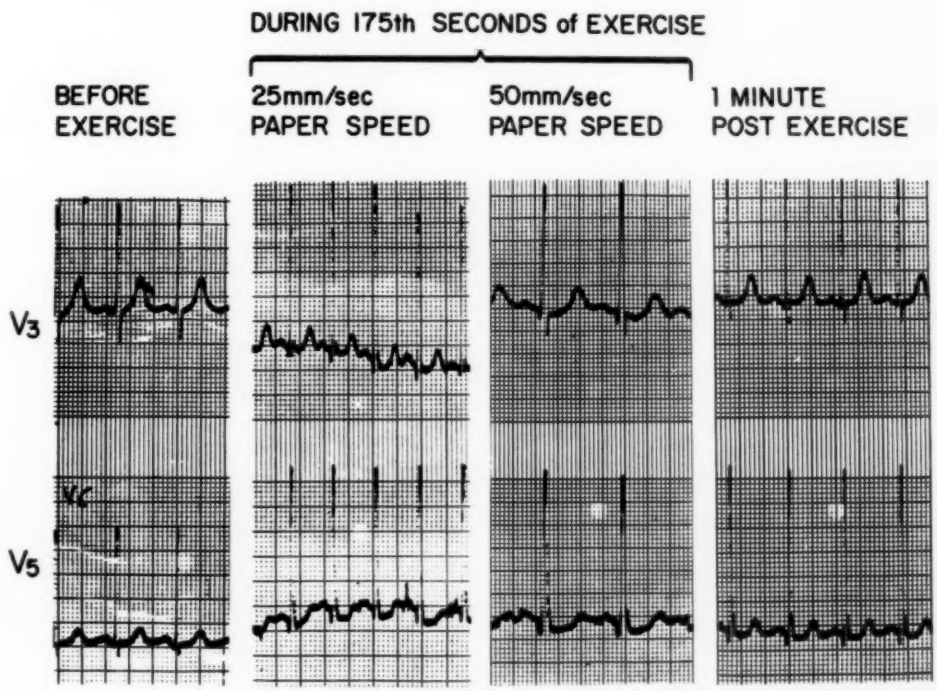


FIG. 10. ST-segment changes during exercise, and disappearance one minute after completion of exercise.

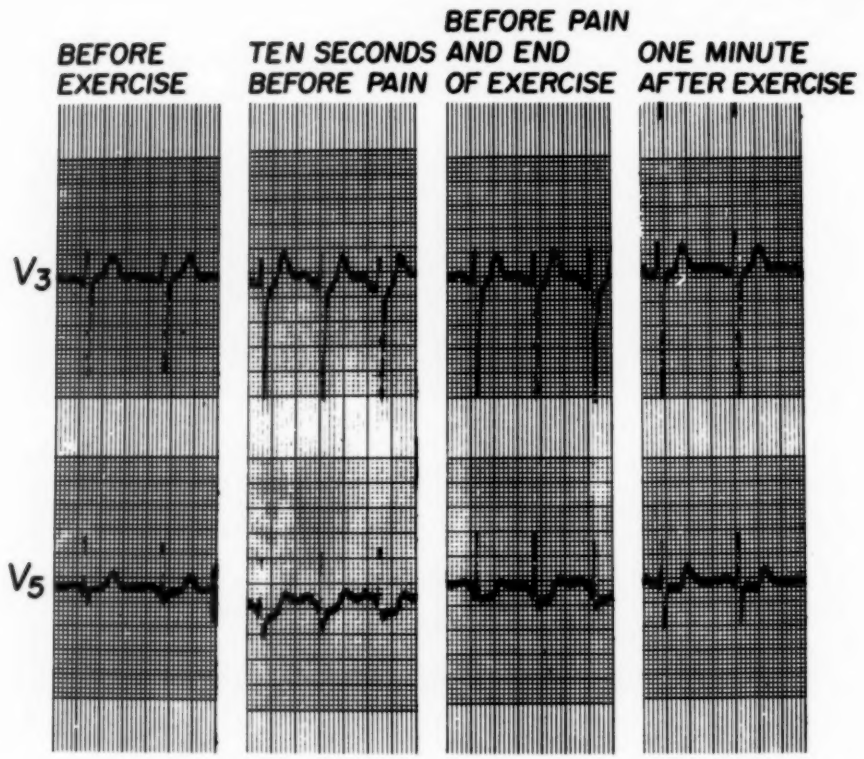


FIG. 11. Significant ST-segment changes ten seconds after starting exercise in a 58-year-old woman with hypertensive CV disease without angina. The patient experienced pain in the post-exercise period, in the absence of ST-segment changes.

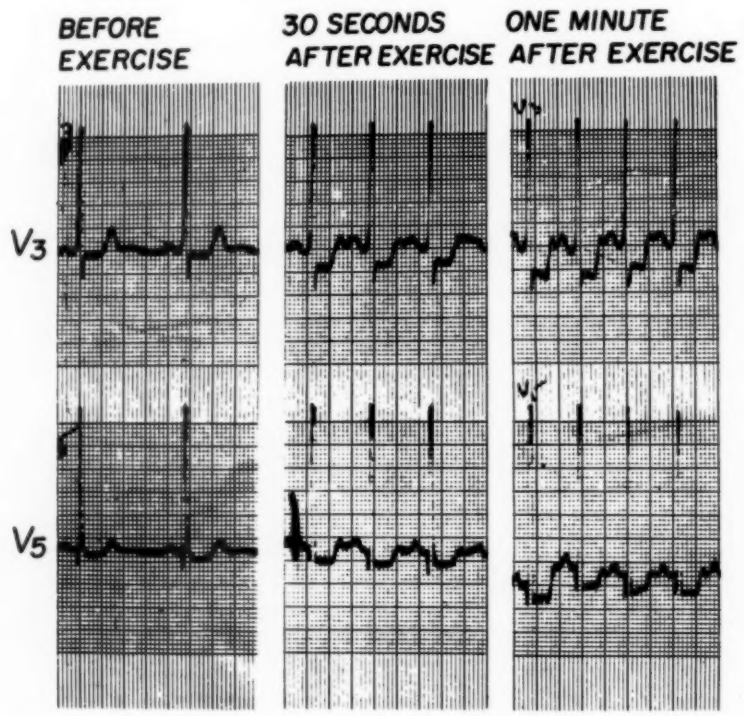


FIG. 12. Electrocardiogram showing early onset of ischemic changes during exercise in the patient represented in Figure 11 The alterations in the T-wave occurred in the absence of chest pain.

Artifacts are produced when: 1) the patient is touched, 2) connections are loose and cause poor skin electrode contact, 3) electrodes have slipped, 4) the patient's elbows or hands strike electrode attachments, 5) the patient is a woman with pendulous breasts, and 6) the ensiform process cannot be identified. Other sources of error against which precautions should be taken are outlined in the section on Technic.

Figure 7 shows the close similarity of precordial electrocardiograms obtained with the conventional system and the EEP system. Figure 8 illustrates how little the position of the heart alters the tracings obtained by the two methods.

Figure 9 (left) is an example of the precordial tracings obtained by the usual method during continuous exercise in a geriatric patient with muscle tremor such as is seen in Parkinson's disease; satisfactory electrocardiographic study was precluded because of muscle artifacts. The tracing on the right illustrates the

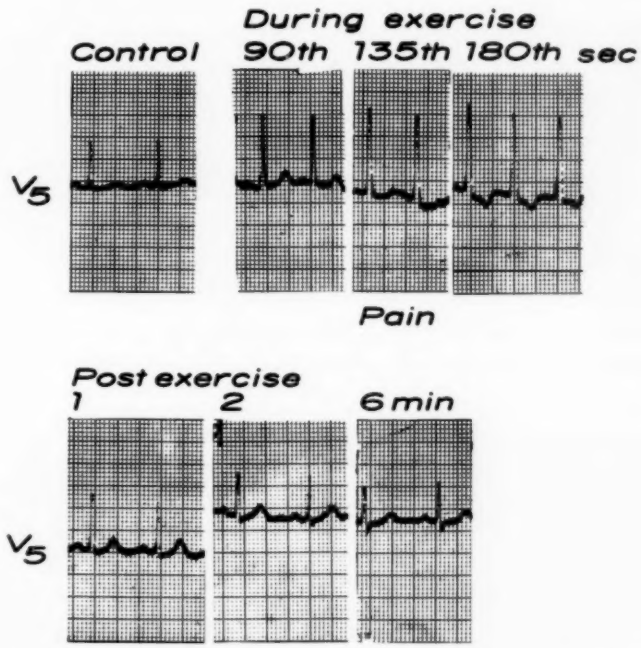


FIG. 13. Significant ST-segment and T-wave changes developing along with the onset of pain during exercise but disappearing immediately after exercise.

FIG. 14. Arrhythmia during exercise (not noted after exercise), in a 46-year-old man who had suffered a myocardial infarction four years previously.

improvement in the technical quality of the electrocardiogram obtainable by the EEP system in a patient with parkinsonism. Standard and unipolar extremity leads of similar quality can be obtained by attaching the cupped precordial electrodes to the right and left acromial processes and the spine of the fifth lumbar vertebra respectively, and then proceeding as with the standard leads.

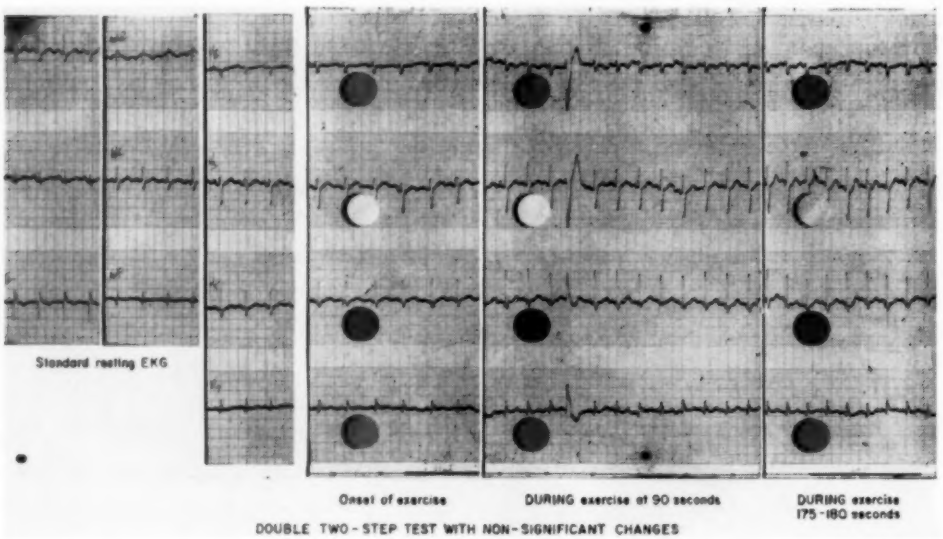

Standard resting EKG
Onset of exercise
DURING exercise at 90 seconds
DURING exercise 175-180 seconds
DOUBLE TWO-STEP TEST WITH NON-SIGNIFICANT CHANGES

FIG. 15. Exercise without ischemic cardiac changes (double two-step test) one year after diaphragmatic myocardial infarction.

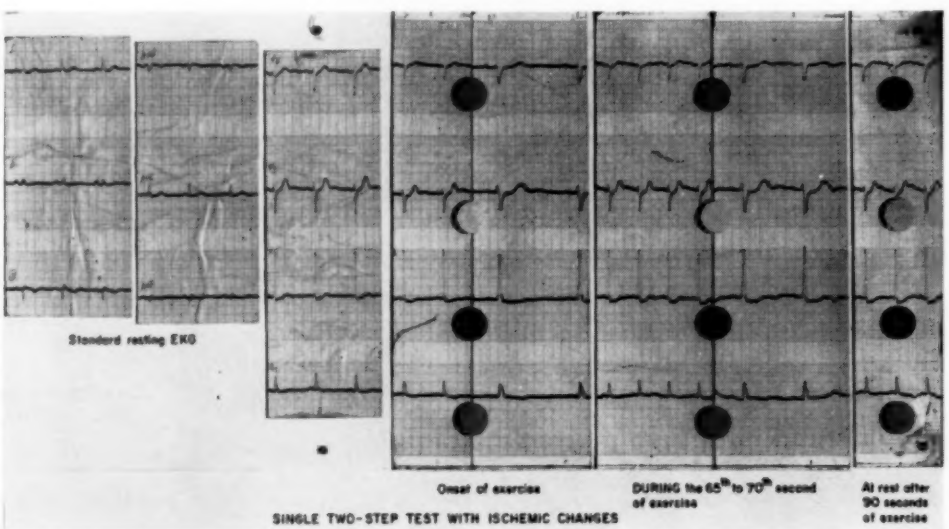

Standard resting EKG
Onset of exercise
DURING the 65th to 70th second of exercise
At rest after 90 seconds of exercise
SINGLE TWO-STEP TEST WITH ISCHEMIC CHANGES

FIG. 16. Appearance of ischemic changes during exercise (single two-step test) one year after diaphragmatic myocardial infarction.

Figure 10 illustrates a common difference between electrocardiograms recorded during and after exercise. In 95 per cent of our tracings in which ST-segment changes occurred, the changes were maximal during the performance of exercise, and in 25 per cent they disappeared immediately after exercise and were not seen at any time during the post-exercise period.

Figures 11 and 12 illustrate the early onset and persistence of ischemic changes during exercise in a 58-year-old female with hypertensive cardiovascular disease without angina. Changes began ten seconds after starting exercise and reached a maximum after one minute of exercise. Pain appeared only in the post-exercise period (Fig. 11). This illustrates an important safety feature of the EEP technic; the test can be discontinued if warranted by the ST-segment changes, before the development of pain. In almost all such patients the exercise electrocardiogram was distinctly abnormal prior to the appearance of pain.

Figure 13 illustrates distinct ST-segment and T-wave changes indicative of pain during exercise; pain was not present at any time during the post-exercise period.

Significant arrhythmias were uncommon during exercise, but APC, VPC and ventricular tachycardia were noted. Figure 14 shows ventricular extrasystoles alternating with regularly conducted beats in a 46-year-old white male who had suffered a myocardial infarction four years before. Occurrence of such an arrhythmia during exercise would probably warrant discontinuance of the test. This kind of evidence of increased myocardial instability during stress indicates the need for special precautions during anesthesia and major surgery. An interesting observation was the response during exercise of patients with healed myocardial infarctions, as shown in Figures 15 and 16. Both patients had sur-

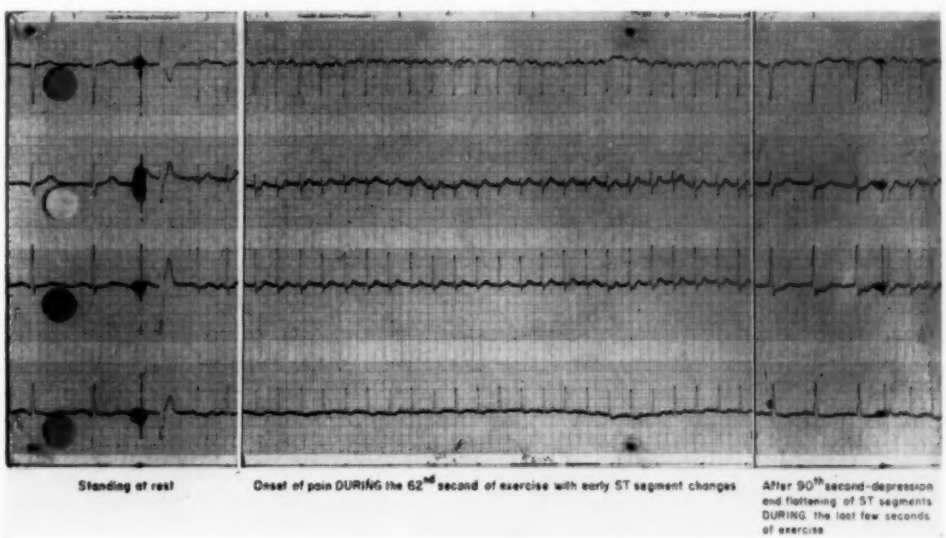

Standing at rest
Onset of pain DURING the 62nd second of exercise with early ST segment changes
After 90th second-depression and flattening of ST segments DURING the last few seconds of exercise

FIG. 17. Absence of pain during exercise in a patient taking an MAO inhibitor for three weeks. While the patient was receiving placebo medication, pain was present during and after exercise.

TABLE 1

Electrocardiographic Changes during Exercise in 176 Persons without Heart Disease

(A) RS-T SEGMENT		
1) Flat ST segment depressions up to 1.5 mm.	10	5.7%
2) Sagging ST segment depressions up to 1.0 mm.	7	4.0%
3) Junctional ST segment depressions up to 3.5 mm.	124	70.4%
4) Isoelectric ST segments	17	9.6%
5) ST segment elevations up to 1.5 mm.	18	10.2%
(B) T WAVE		
Higher	64	36.4%
Lower	80	45.4%
Flat	25	14.2%
Diphasic or inverted	7	4.0%
(C) ARRHYTHMIAS		
1) APC's	1	
2) VPC's	1	
3) APC's and VPC's	1	
Maximum RS-T changes and leads in which noted:		
V_E		11%
V_3		47%
V_5		78%
V_7		21%

vived a diaphragmatic myocardial infarction one year previously. One (Fig. 15) was relatively asymptomatic and had no pain while performing the exercise test; the other patient (Fig. 16), who required 6 to 10 nitroglycerin tablets per day, manifested evidence of cardiac ischemia during exercise. The difference in responses might indicate adequate collateral circulation in the patient represented in Figure 15, and continuing coronary insufficiency in the patient represented in Figure 16.

DISCUSSION

A technic has been described for recording the electrocardiogram during exercise. This technic furnishes tracings free of baseline shift and muscle potential. No special electrocardiographic equipment is required for the performance of this test. It is safe, since the exercise can be stopped at the first evidence

of myocardial ischemia or abnormal cardiac rhythm. Interpretable tracings can be obtained even in the presence of severe muscle tremors.

The detection and the significance of changes during exercise are under continuing study. The fact that changes in the ST-segment and T-wave are most marked during exercise and are frequently completely absent in the post-exercise period may permit better evaluation and quantitation of known ischemic heart disease and earlier detection of the occult form. Another application of this technic is in the study of the influence of environment and various therapeutic measures on the electrocardiogram during exercise.

Preliminary studies have shown that nitroglycerin and monoamine oxidase (MAO) inhibitors may sometimes modify the electrocardiographic response during exercise, as demonstrated in Figure 17. Further studies in the evaluation of pharmacologic agents may show this technic to be useful, since the electrocardiographic changes are more marked during exercise than in the post-exercise period. Additional correlative studies are now in progress.

In precordial electrocardiograms recorded during and throughout exercise in over 300 patients, the ST-segment alterations were maximal in V_3 and V_5 during and near the end of exercise. It was perhaps significant that 90 per cent of these changes started to revert toward control levels within five to thirty seconds after the termination of exercise. Thus the maximal changes produced by exercise were evident before the usual time of recording post-exercise electrocardiograms.

Table 1 shows the normal variations in the electrocardiogram during exercise in 176 normal patients, although incomplete, showed the following: in 80 per cent the heart rate ranged from 100 to 150 per minute during exercise; in 5 per cent the rate was 160 or more. The extent and pattern of the changes in ST-segment and T-wave could not be correlated with the age of the patient or the heart rate. Junctional ST-segment depression up to 3.5 mm. occurred in 70 per cent of the electrocardiograms, flat ST-segment depression up to 2 mm. in 6 per cent, and sagging up to 1 mm. in 4 per cent. In 10 per cent the ST-segment was iso-electric or elevated up to 1.5 mm. Inverted or diphasic T-waves were seen in only 4 per cent. In the remainder, T-wave changes were insignificant, the waves being a few millimeters taller or shorter than those recorded in the resting state. In our study of normal subjects, extrasystoles were infrequent, appearing in only 3 of the tests. When changes did appear, they were most often seen in leads V_5 and V_7, less frequently in V_3, and rarely in V_1.

An important point is the early waxing and waning of ST-segment abnormalities, several seconds or even one to two minutes before they become fixed. These early changes are almost always followed by significant abnormalities, and are not based on changes in the respiratory rate.

SUMMARY AND CONCLUSIONS

A technic has been developed which provides electrocardiographic tracings relatively free of baseline shift and interference from muscle potentials during and throughout exercise.

The procedure offers the advantage of safety, since exercise can be stopped at the first electrocardiographic evidence of abnormality.

The test can be performed with any electrocardiographic machine without additional electronic equipment.

The precordial tracings obtained by this system are comparable to those obtained with the Wilson central terminal.

The technic makes possible the detection of relatively transient electrocardiographic abnormalities that may be present during exercise but not afterward.

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PANEL DISCUSSION ON THE TREATMENT OF CARDIAC ARRHYTHMIAS

Moderator: JOHN M. EVANS, M.D.*
Washington, D. C.

It is our hope this afternoon to maintain as high a level of performance as that of this morning's session. In this we have a good start: among our speakers we have not only family physicians and clinical investigators, but also a basic scientist, Dr. Robert Moe from the Pharmacology Department of Hoffmann-La Roche in Nutley, New Jersey. The other members of our panel are Dr. William Likoff, Clinical Professor of Medicine at Hahnemann Medical College and Hospital of Philadelphia, Dr. Irwin H. Ardam, Clinical Instructor in Medicine at the George Washington University Medical School in Washington, D. C., Dr. Robert Green, Department of Medicine at the University of Cincinnati Medical School, and Dr. W. Proctor Harvey, Associate Professor of Medicine at Georgetown University, Washington, D. C.

A COMPARISON OF SOME CARDIAC RESPONSES TO RO 2-5803 (RYTHMOL), QUINIDINE AND PROCAINE AMIDE IN LABORATORY ANIMALS†

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For more than forty years quinidine has been employed for its favorable effects on the rhythm of the heart. Procaine amide, still a controversial compound, also has gained recognition during the past ten years for its cardiac effects, particularly when used intravenously.

A relative newcomer is 2,6-bis(1-piperidylmethyl)-4-(a,a-dimethylbenzyl) phenol dihydrobromide, or Rythmol[1], previously designated as Ro 2-5803. It also shows promise of having a place in the ranks of the cardio-regulators (1).

Numerous publications, reviewed by such authorities as Bellet *et al.* (2, 3) Gold (4), Kayden *et al.* (5) and others, emphasize that the therapeutic effectiveness of anti-arrhythmic preparations in humans is not completely predictable. The same unpredictability during experimental work on animals accounts for the varying degrees of responsiveness to anti-arrhythmic drugs. Some of these responses have been considered as toxic manifestations; however, they may also be recognized as the essential action of the drug on cardiac muscle.

Gold (4), in 1950, suggested that the single action of quinidine which probably

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† Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November 3, 1960.

[1] Trademark of Hoffmann-La Roche Inc.

TABLE 1

Pharmacodynamic Effects Common to Procaine Amide, Quinidine and Ro 2-5803

(Qualitative observations on laboratory animals)

A. Increased threshold for stimulation
B. Prolonged refractory period
C. Weak atropine-like action
D. Negative inotropic action
E. Local gastro-intestinal irritation (occasional)
F. Hypotensive (partly vascular) action when injected intravenously
G. Central nervous system action with near lethal doses (not confirmed with Ro 2-5803)
H. Increased cardiac intracellular potassium (not confirmed with procaine amide

TABLE 2

Acute Toxicity of 3 Cardiac Depressants in Mice

Drug	LD_{50} (mg./Kg.)		
	Intravenously	Intraperitoneally	By mouth
Procaine amide	111	378	562
Quinidine sulfate	54	263	535
Ro 2-5803*	30	156	330

* Rythmol, T. M.

TABLE 3

Comparative Potency of 3 Cardiac Depressants in Representative Tests

	Procaine Amide	Quinidine Sulfate	Ro 2-5803
A. Isolated auricles—rabbit (Dawes method) ED_{30} (Gm./ml./bath)	1.6×10^{-6}	2.6×10^{-6}	0.7×10^{-6}
B. Anti-acetylcholine-induced atrial fibrillation—dog ED_{50} (mg./Kg., i.v.)	8.0	1.1	1.0
C. Anti-epinephrine-induced arrhythmia—dog ED_{50} (mg./Kg., i.v.)	2.5	1.0	1.0

accounts for many of its therapeutic applications in disorders of cardiac rhythm, is to increase the refractoriness of the various cardiac structures. Other authors (6, 7) have coupled this action with an increased threshold of tissue excitation.

The differences among the three cardiac depressants—quinidine, procaine

amide and Rythmol—as shown by their pharmacologic effects in laboratory animals are, for the most part, quantitative.

PHARMACOLOGIC EFFECTS

The pharmacologic effects common to the three compounds by *in vivo* and *in vitro* tests are shown in Table 1.

The LD_{50} values obtained for each of 3 routes of administration (intravenous, intraperitoneal and by mouth) demonstrate the relative toxicities of the 3 preparations (Table 2). The toxicity of the drugs in these high doses may be taken as crude indices of their respective pharmacologic effects on the heart itself, since the major action of each drug is on cardiac tissue.

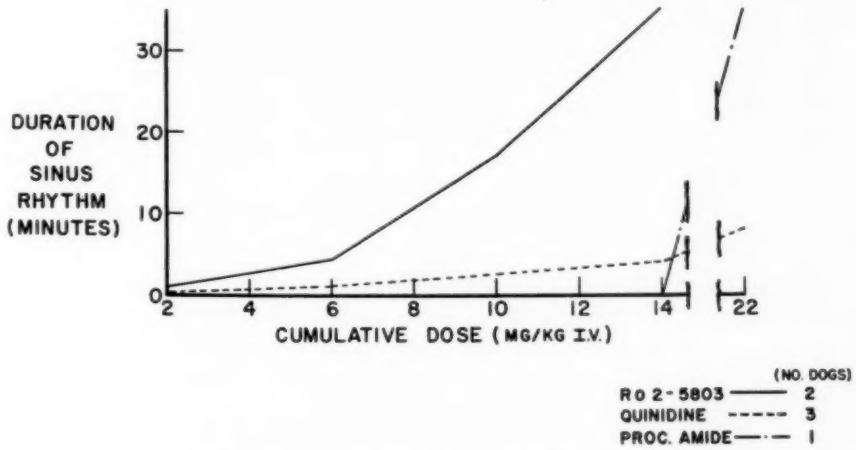

FIG. 1. Effect of repeated intravenous injections of Rythmol (Ro 2-5803), quinidine and procaine amide on ouabain-induced cardiac arrhythmias in dogs.

TABLE 4

Electrolytes in the Total Heart of the Rat

(Drug administered as 2 equal intraperitoneal injections two hours apart)

Drug	Total Dose (mg./Kg.)	Mean Body Weight	Electrolyte Conc. One Hour after Second Dose (mEq./Kg. fat-free dry tissue)		K/Na Ratio*
			Potassium	Sodium	
Control (H_2O)	(2 ml./Kg.)	159	100.6	68.2	1.475
Quinidine sulfate (EtOH sol.)	120	156	107.5	61.2	1.757
Ro 2-5803/1† (aq. sol.)	120	159	108.0	63.0	1.714

* By "*t*" test: Controls *vs.* Quinidine—$P < .001$
Controls *vs.* Ro 2-5803/1—$P < .05$
Quinidine *vs.* Ro 2-5803/1—not significant

† Rythmol, T. M.

Results of some pharmacologic tests in animals are as follows (Table 3):

A. The refractory period to repeated stimuli in electrically driven isolated auricles of rabbits was prolonged by each of the compounds. The relative activity of each drug is determined by the concentration required to produce the ED_{30}; with this test, Rythmol was more effective than either quinidine or procaine amide.

B. Acetylcholine-induced auricular flutter in open-chest experiments on anesthetized dogs demonstrated that Rythmol and quinidine were equally effective in reducing the auricular tachycardia.

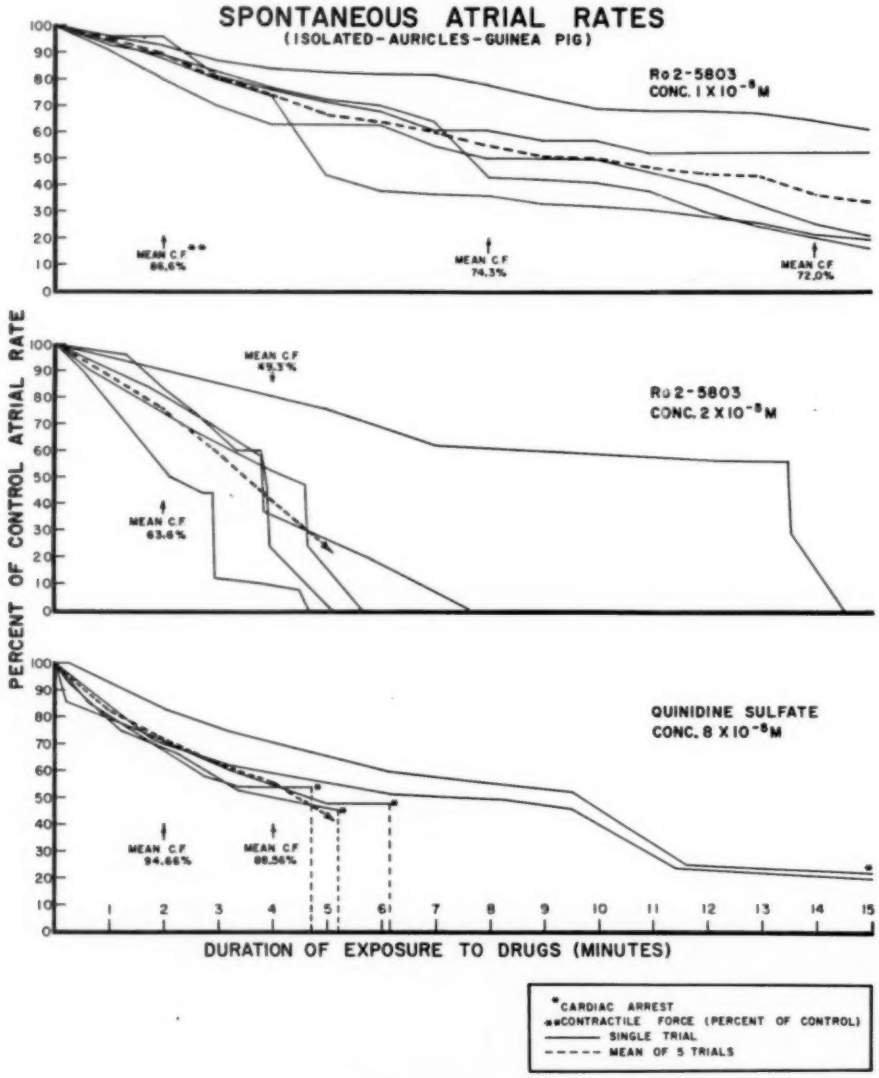

FIG. 2. Effects of Rythmol (Ro 2-5803) and quinidine in decelerating the isolated spontaneously-beating auricle of the guinea pig.

C. In anesthetized dogs with epinephrine-induced arrhythmia (primarily ectopic ventricular beats), quinidine and Rythmol intravenously were equally active and each was more effective than procaine amide (Fig. 1).

An intravenous dose of 100 μg. of ouabain per Kg. in dogs induced complexes of atrial and ventricular ectopic beats, cardiac acceleration and increased blood pressure. Repeated doses of quinidine, procaine amide or Rythmol were given intravenously and the cumulative effects observed. The respective doses were 2, 4 and 8 mg. per Kg. administered at thirty-minute intervals. Rythmol was effective against this type of experimental arrhythmia whereas neither quinidine nor pro-

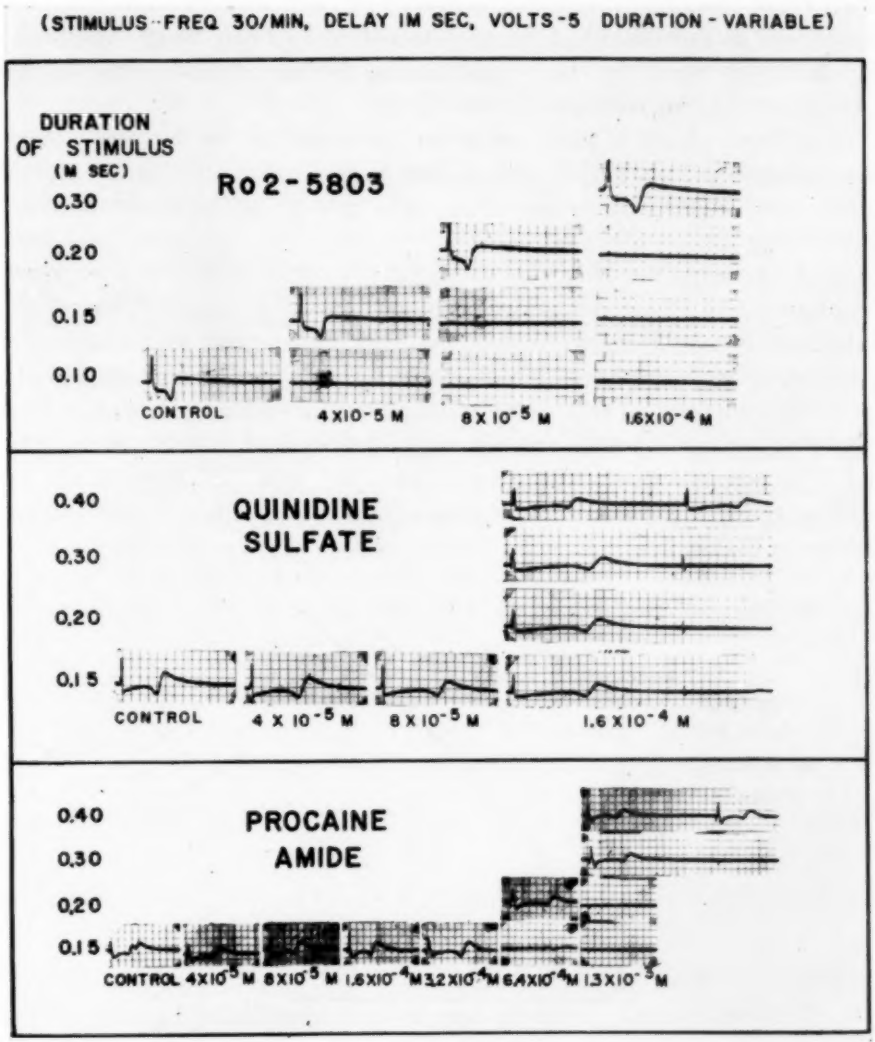

FIG. 3. Effects of Rythmol (Ro 2-5803), quinidine and procaine amide on conduction patterns and duration of the required stimulation in isolated papillary muscle from the right ventricle of the cat.

caine amide had a significant effect until cumulative doses of 14 mg. per Kg. or more were reached. Although procaine amide in the higher doses regularized the rhythm, it did not decelerate the tachycardia. Rythmol and quinidine, on the other hand, both exerted a slowing action on the heart rate.

Since ouabain intoxication may be associated with decreased intracellular potassium in cardiac muscle, the relative effectiveness of Rythmol and quinidine could well be related to their ability to modify ionic levels within cardiac tissue (Table 4). We therefore investigated the effects of Rythmol and quinidine on the total sodium and potassium levels in the rat heart at one hour after the second of two intraperitoneal injections of Rythmol or quinidine. The total dose given within a three-hour test period was 120 mg. per Kg. Intracellular potassium was increased and intracellular sodium was decreased by both drugs. The potassium-sodium ratios induced by these compounds, though similar, were significantly different from the control value (Table 4).

Rythmol was about 4 times as active as quinidine in decelerating isolated spontaneously beating auricles of guinea pigs. Under these same conditions, however, the negative inotropic effect was greater with Rythmol than with quinidine (Fig. 2).

Isolated papillary muscle from the right ventricle of cats was suspended between stimulating electrodes and electrograms were recorded. Control patterns of excitation thresholds were obtained by using an electrical source of 5 volts with a frequency of 30 per minute. The duration of the stimulus was employed as the variable. The duration of treatment, within the immersion fluid, was five minutes. The fluid was then removed, the threshold determined, and an electrogram obtained. The changes in the duration of the "R" and "T" conduction patterns and the increase in duration of the stimulation required to produce the patterns are shown in Figure 3.

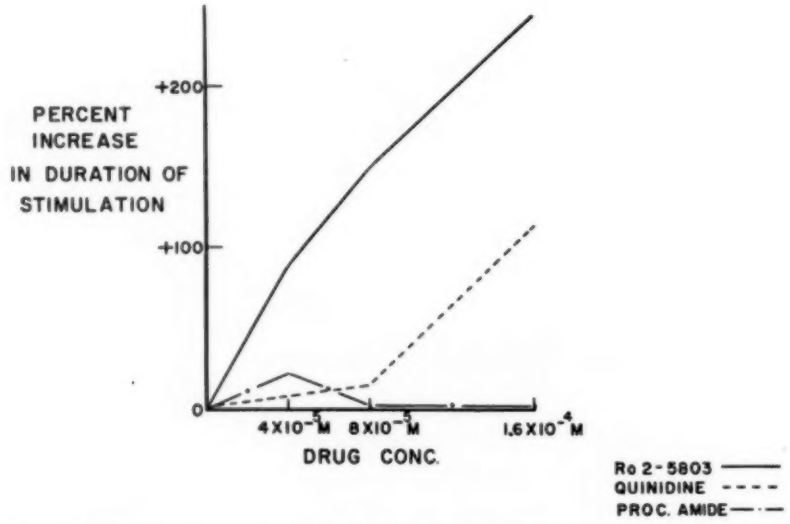

FIG. 4. Effects of Rythmol (Ro 2-5803), quinidine and procaine amide on the stimulation threshold in the isolated papillary muscle of the cat.

The threshold of excitation of these isolated papillary-muscle preparations was increased after treatment with Rythmol and with quinidine as shown in Figure 4. When the increase in the duration of stimulation was expressed in terms of percentage change, Rythmol was substantially more effective than quinidine. In contrast, procaine amide was ineffective at these concentrations.

SUMMARY

Pharmacologic findings indicate that many of the differences between Rythmol, quinidine and procaine amide, as modifiers of cardiac tissue, are quantitative rather than qualitative. Rythmol, in general, exerts a greater effect than either quinidine or procaine amide. However, because of the nature of this activity, the true efficacy of Rythmol can be determined only by study in patients with cardiac arrhythmia rather than in animals.

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A NEW ANTI-ARRHYTHMIA AGENT (RO 2-5803): ITS EFFECT ON VENTRICULAR ARRHYTHMIAS*

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Within recent years important advances have been made concerning the genesis and pathophysiology of cardiac arrhythmias. As a consequence, treatment has become more precise. This is particularly true of the counterbalancing measures for digitalis toxicity and electrolyte imbalances.

* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November 3, 1960.

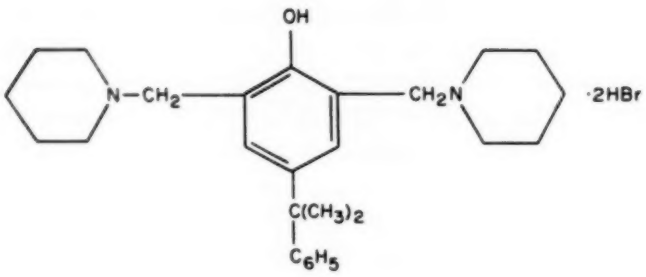

FIG. 1. Chemical formula of Ro 2-5803

The urgent need for acceptable and efficient agents in the treatment of abnormal rhythms, however, has not been fully satisfied. Although quinidine and either digitalis or its glycosides are the keystones of any serious therapeutic regimen, there remains a wide variety of clinical circumstances under which less toxic, more acceptable and critically effective drugs could be used.

This discussion attempts to establish the actual and potential usefulness of a new agent,[1] Ro 2-5803, in the treatment of ventricular arrhythmias. The experience in this specific area is preceded by a review of the cases, and the methods of administration employed in the treatment of a broader variety of cardiac arrhythmias.

The formula for Ro 2-5803 is indicated in Figure 1. The clinical pharmacology and earlier experiences with the preparation have been reported in a previous communication (1).

CLINICAL MATERIAL

One hundred and eleven patients were treated with Ro 2-5803 (Fig. 2). Ages ranged from 16 to 71, with an average of 52.4 years. The etiologic types of heart disease were as follows: rheumatic 45, atherosclerotic 41, hypertensive 12, and congenital 5; no evidence of an organic cardiac disorder was demonstrated in the remaining 8 patients.

As shown in Figure 2, among the cases of rheumatic heart disease the arrhythmia was supraventricular in 31, ventricular in 8, and of the combined type in 6. Among the cases of atherosclerotic heart disease the arrhythmia was supraventricular in 7, ventricular in 30, and of the combined type in 4. In the hypertensive group of patients, 2 had supraventricular, 9 ventricular, and 1 a combined type of arrhythmia. Each of the patients with a congenital cardiac lesion had supraventricular arrhythmia. Among the patients who did not have demonstrable heart disease, 1 had supraventricular, 6 ventricular, and 1 a combined type of abnormal heart action.

In summary, a total of 58 supraventricular and 65 ventricular arrhythmias were observed and treated.

METHODS

One hundred patients received Ro 2-5803 orally (Table 1). The dose ranged from 400 to 3200 mg. and averaged 1000 mg. per day. The medication uniformly was offered in four

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[1] Ro 2-5803 (Rythmol) is a product of Hoffmann-LaRoche Inc., and is to be marketed as Rythmol.

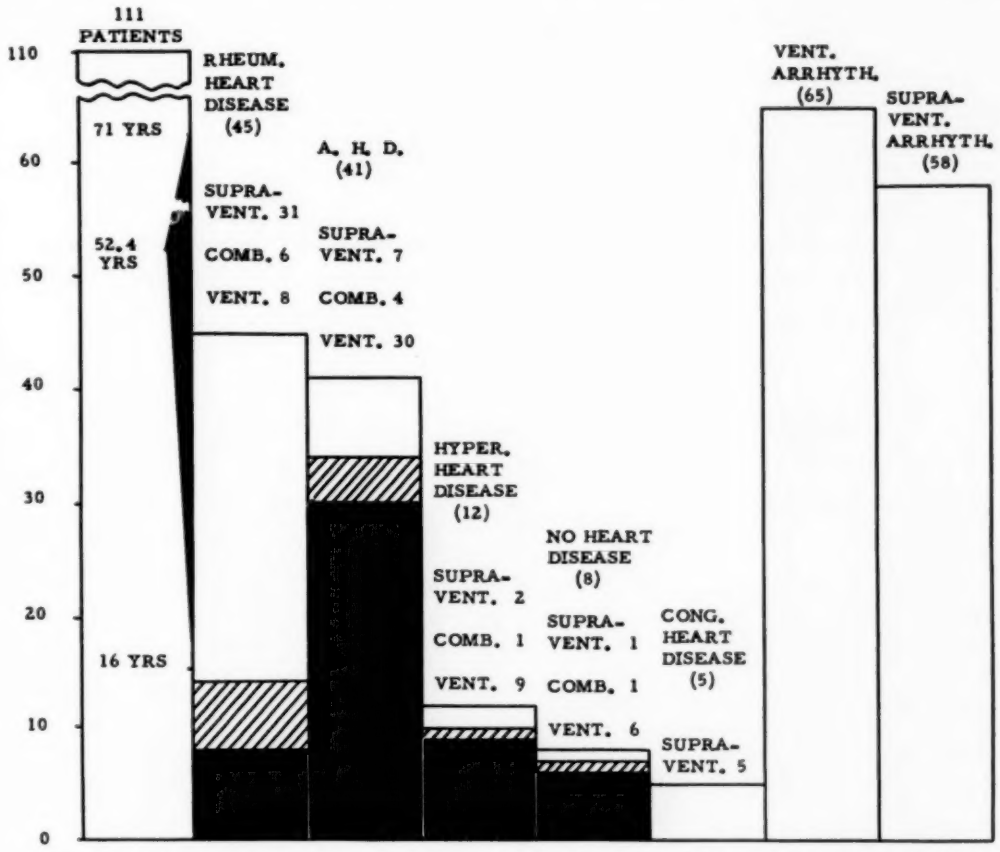

FIG. 2. Distribution of various cardiac arrhythmias among 111 patients treated with Ro 2-5803. Height of column = number of patients. In columns 4–6, the white area denotes patients with supraventricular arrhythmia; the cross-hatched area denotes those with a combined type; and the black area denotes those with ventricular arrhythmia. The last two columns represent the total number of cases of ventricular and of supraventricular arrhythmias in the group.

TABLE 1

Methods of Administration and Dosage of Ro 5-2083

Method	No. of Patients	Dose (mg.)		Duration of Treatment	
		Range	Average	Range	Average
Intravenous	11	100–500	200	20–100 mins.	—
Oral	100	420–3200 daily	1000 daily	17–217 days	53 days

equally divided doses daily over a period ranging from seventeen to two hundred and seventeen days (average, fifty-three days).

Eleven patients were treated with the intravenous preparation. The dose ranged from 100 to 500 mg., and averaged 200 mg. The duration of the infusion ranged from twenty to one hundred minutes (Table 1).

RESULTS

The types of arrhythmia that were classified as ventricular and the effects of oral and intravenous administration of Ro-2-5083, are shown in Table 2. No patient with ectopic ventricular contractions was accepted for treatment unless a minimum of 20 per cent of the cardiac contractions originated from an abnormal focus over a period of three minutes.

The electrocardiographic effect of 100 mg. of Ro 2-5803 administered intravenously to a patient with bigeminal rhythm as a result of recurring ectopic ventricular contractions is illustrated in Figure 3.

TABLE 2

Results of Ro 5-2083 Therapy in Ventricular Arrhythmias (Acute and Chronic)

Type of Arrhythmia	Total No. of Patients	Effect of Ro 5-2083 Given Intravenously			Effect of Ro 5-2083 Given Orally		
		Correction of arrhythmia	Mod. effect	None	Correction of arrhythmia	Mod. effect	None
Ventricular tachycardia	6				3		3
Ectopic systoles	59	1		2	41	8	7
Totals	65	1		2	44	8	10

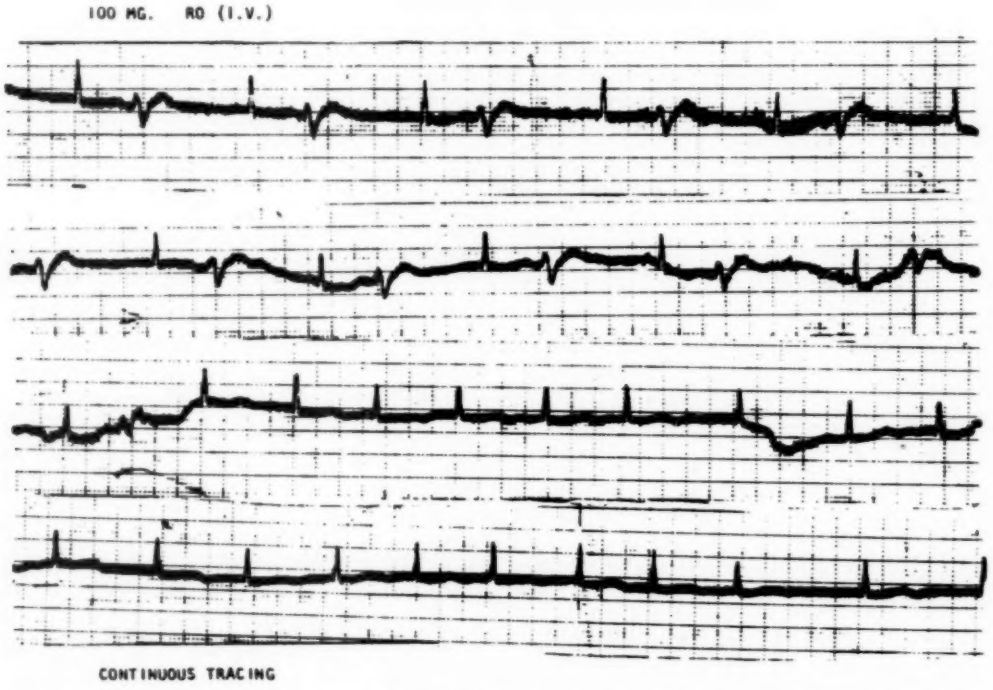

FIG. 3. The ECG response to a single 100-mg. intravenous dose of Ro 2-5803 in a patient with bigeminal rhythm as a result of ectopic ventricular contractions.

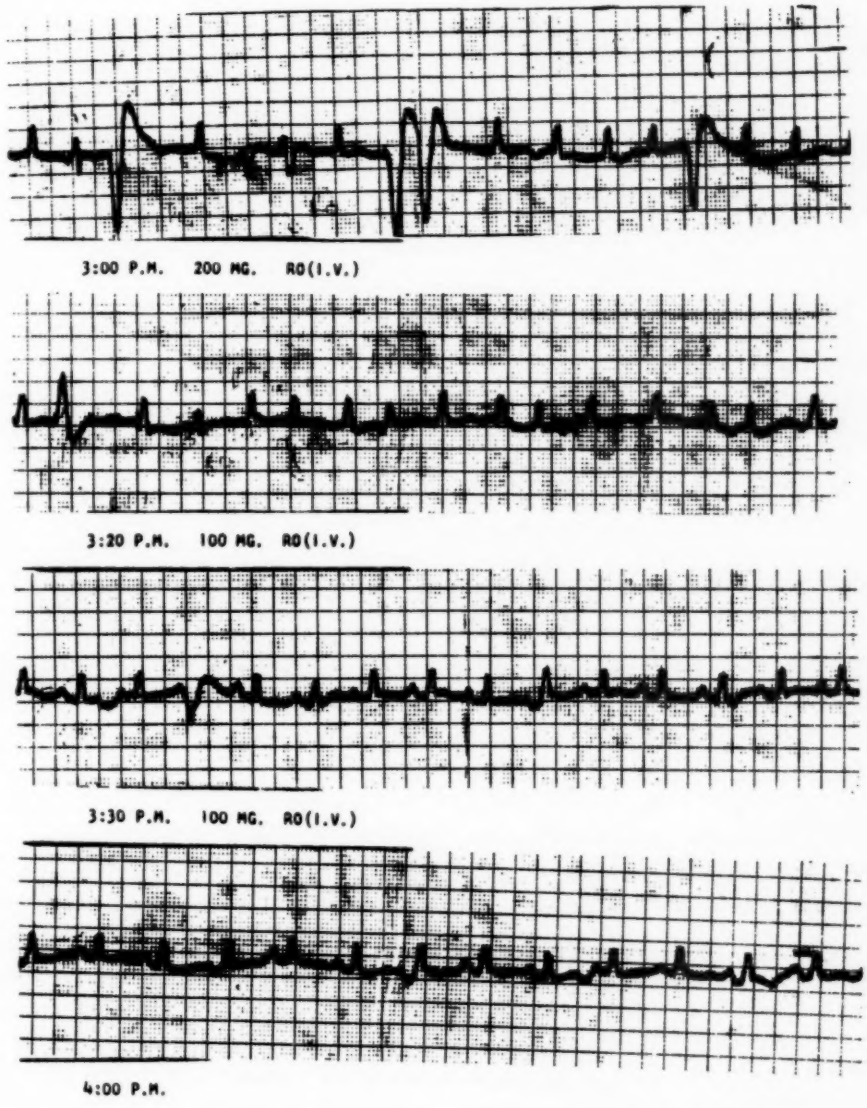

FIG. 4. The ECG response of frequent ectopic ventricular contractions occasionally arising in pairs, to repeated intravenous doses of Ro 2-5803.

An equally effective electrocardiographic response to the intravenous preparation may be observed in Figure 4 which depicts the disappearance of frequent ectopic ventricular contractions, occasionally arising in pairs, after repeated injection of Ro 2-5803.

The effectiveness of the oral preparation of Ro 2-5803 in terminating serious ventricular arrhythmia is illustrated in Figure 5. The electrocardiogram demonstrates the sudden cessation of ventricular tachycardia while the patient was under treatment.

The most severe toxic manifestations of Ro 2-5803 were observed when this agent was given intravenously. Although highly effective when administered

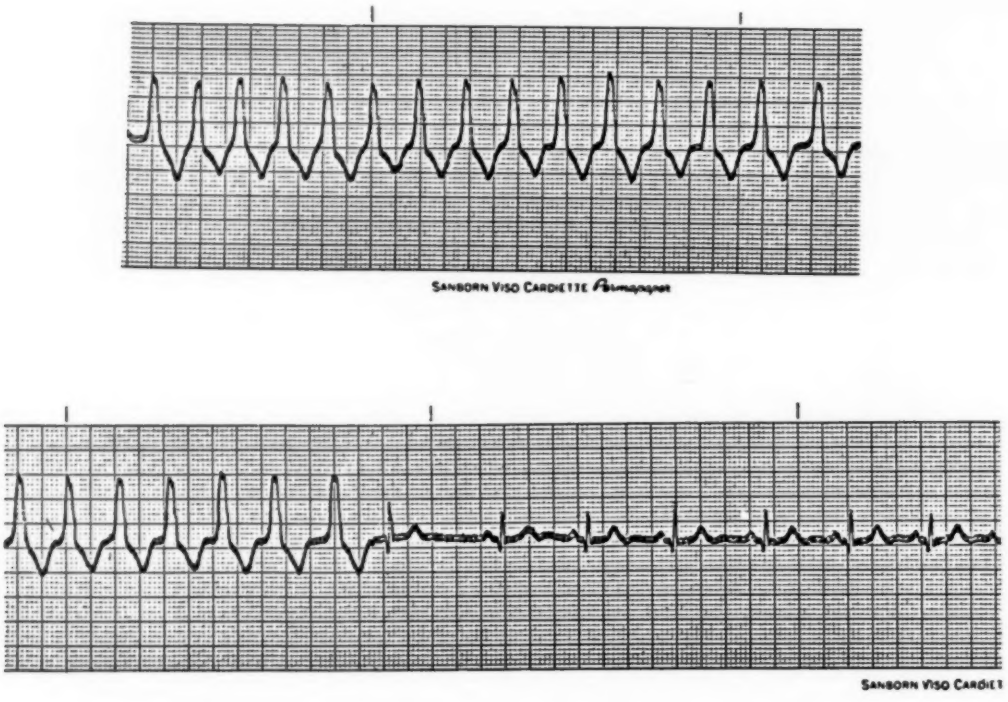

FIG. 5. The ECG response of ventricular tachycardia to orally administered Ro 2-5803.

by this route, the drug may cause serious prolongation of the intraventricular conduction time if relatively large quantities are given within a short period of time. This summation effect to toxic levels may precede the correction of the arrhythmia or may persist for a considerable period after the rhythm has returned to normal. If, however, the compound is given in single doses at intervals of three to four hours, intravenous administration appears to be safe and effective.

The efficacy of Ro 2-5803 by the oral route has made the need for parenteral administration unusual in our experience. No toxic effects were observed when Ro 2-5803 was used orally. The most common side-effects were nausea, vomiting and dryness of the mouth; dermatitis was rare. Of these symptoms the most disturbing was nausea, but it rarely developed to serious proportions or necessitated the cessation of treatment. Dermatitis occurred in only 1 patient—as a blotchy erythematous rash, which disappeared promptly on withdrawal of the drug.

COMMENT

The foregoing observations show that Ro 2-5803 is an effective agent in the treatment of acute and chronic ventricular arrhythmias.

When administered orally in an average dosage of 400 mg. four times a day, it is extremely effective in the treatment of ectopic systoles. This has an important application when ectopic ventricular rhythms develop in patients with serious rheumatic, atherosclerotic or hypertensive heart disease.

Oral administration of Ro 2-5803 also is effective in patients with paroxysmal ventricular tachycardia. For the treatment of this serious arrhythmia the dosage schedule may be increased to as much as 800 mg. four times daily.

The side-effects of oral administration are not serious.

Intravenous administration of Ro 2-5803 unquestionably produces a more rapid and effective result. However, there is always the danger of an increase in the intraventricular conduction time. This possibility limits the use of the drug intravenously.

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PERSONAL EXPERIENCES WITH ARRHYTHMIAS*

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The subject of arrhythmias introduces a wide field for remarks on personal experiences in the practice of medicine. Such observations do not lend themselves to statistical analysis and do not justify a scientific paper, but they may prove of value to others.

FACTORS IN SUCCESSFUL MANAGEMENT

Our most important observation, either as clinician, onlooker or critic, is that the principal factor in determining success or failure in the management of arrhythmias is the *composure of the physician*. Our opinions are so strong in this regard that we have established the following 7 basic rules to insure this composure, and insist on strict adherence to these rules for ourselves and those associated with us:

1. A precise clinical evaluation.
2. Treatment of the whole patient, not just the arrhythmia.
3. "Skillful neglect" rather than overtreatment.
4. An up-to-date knowledge of drugs.
5. The use of only one drug at a time.
6. Formulation of a plan of action in advance.
7. Availability of adequate ancillary equipment.

1. *Clinical evaluation*

In the clinical evaluation of the patient, frequently the history offers the only clue to the problem: Was the onset of rapid heart action sudden or gradual? Did

* Presented at the Symposium on Current Topics in Cardiovascular Disease, Washington, D. C., November 3, 1960.

† Director.

it cease abruptly? Was the heart beat regular or irregular? Could the arrhythmia be stopped? The history also furnishes necessary information as to the natural progress of the arrhythmia, prior medication, and the existence of precipitating causes such as hyperthyroidism or rheumatic heart disease.

Our standard procedure in the clinical evaluation is first to establish a working impression of the arrhythmia from the history alone, and then from the history and physical examination, at which time we predict what the electrocardiogram will demonstrate. It is remarkable how often these predictions coincide with the electrical facts. The value of this discipline is most evident when one is confronted with these problems of nature in the field of practice rather than in the medical school.

An exact electrocardiographic diagnosis should be made whenever possible. However, there is danger of interpreting arrhythmia incorrectly on the basis of short strips of tracing, without the diagnostic assistance from such simple techniques as vagal stimulation or exercise. A part of the first basic rule, therefore, is an exploration of the patient to find the area from which the necessary diagnostic components of the electrocardiogram best may be determined, and to obtain a tracing that is long enough for precise analysis of the arrhythmia.

2. *Treatment of the whole patient*

Auricular fibrillation in a patient with thyrotoxicosis offers an excellent example for treatment of the whole patient rather than the arrhythmia alone.

3. "*Skillful neglect*"

"Skillful neglect" means that as little as necessary is done with the smallest therapeutic dose of medication administered by the safest route. A drug should never be used intravascularly if an intramuscular injection will suffice, nor intramuscularly if oral administration will accomplish the purpose. An oral dose should never be larger than strictly necessary. We never use any drug we cannot justify.

The value of "skillful neglect" cannot be demonstrated better than by a personal experience as a Research Fellow. During a study of the influence of position and drugs on complete heart block, a small amount of epinephrine was inadvertently injected into a patient's vein. Ventricular tachycardia developed immediately, and then ventricular fibrillation. It is most distressing to recall his statements, "Doctor, what did you do to me? I feel funny. You are killing me! I am dying!" Never before or since has my composure been so threatened, nor has reassurance of the patient been so difficult. Precarious consciousness, abetted probably by tilting to and from a head-down position, plus his totally correct statements as to what we had done, continued for an eternity of some five minutes. Then he made a dying request, "Please give me a cold drink of water." This request was fortunate, as the fibrillation reverted to the original state of complete heart block with the first swallow. Obviously the patient knew better what he needed than we did. We wonder how many fates have been sealed by the intracardiac injection of lethal doses of adrenaline.

Recently we observed ventricular fibrillation in a dog, that started at 10 a.m. and persisted until noon; then all electrical heart action and response ceased. A multiplicity of drugs and external stimuli had been used without success. The dog was considered dead and we left the room. Ten minutes later one of us happened to pass by the table. The heart was beating with a normal sinus rhythm.

4. *Up-to-date knowledge of drugs*

Up-to-date knowledge of any drug that may be used in the treatment of arrhythmias is essential, since we are dealing with a complex situation where one flip of the heart may be the difference between kill or cure, and with powerful medicines that may cause the heart to flip. All of us have made, and observed, wrong decisions in the treatment of arrhythmias, but these mistakes in medical judgment must be kept to a minimum. This can be accomplished only by up-to-date knowledge. For example, digitalis is used in the management of paroxysmal auricular tachycardia. However, auricular tachycardia may be a manifestation of digitalis intoxication. We have reviewed a case in which death probably was hastened by the administration of a full digitalizing dose to a patient who had been digitalized and who had auricular tachycardia with block.

5. *Use of one drug at a time*

Once the problem has been complicated by the desperate use of more than one drug, recovery is rare, and occurs despite rather than because of the physician. As part of this rule, we use a fixed dose schedule as a guide, not as dogma.

The relatively recent introduction of open heart surgery has produced a new species of iatrogenic rhythms. During one of these spectacular procedures, arrhythmia developed, and consequently hyperpotassemia, hypopotassemia, altered pH, vagotonia, and a variety of other imbalances were treated. In all seriousness the surgical resident stated, "Why don't we stop the heart and start over."

6. *Formulation of a plan of action*

The plan of action should be written and answer such questions as: What drug will be used? By what route? What dose? What are the desirable and undesirable endpoints of therapy? The accepted plan of action should not be varied unless it is replaced by another plan similarly conceived.

7. *Availability of adequate ancillary equipment*

Ancillary equipment should consist of a tray of selected drugs, a means of providing an airway, a tank of 100 per cent oxygen, and, when feasible, an external defibrillator and pacemaker. Therapy is monitored with a tracing or oscilloscope.

PHYSICIAN COMPOSURE

Probably the greatest threat to the carrying out of these rules in the treatment of arrhythmias is loss of the physician's composure, resulting from the occasional urgent need to do something immediately. As a consequence, some arrhythmias

that are relatively innocuous are overtreated compulsively. A few examples follow.

The unconscious pulseless patient without heart sounds

A fair question at this time might be, "Well, the physician's composure is all well and good to talk about, but how do you remain composed when suddenly confronted with an unconscious, pulseless patient, in the hospital, in the office, or outside?"

Our results with *open-chest cardiac massage* and *mouth-to-mouth breathing* have been very poor, and we have seen cases in which this widely publicized procedure has been carried out when not indicated. Moreover, opening a chest is not conducive to composure.

External cardiac massage. Animal experiments in 1878 indicated the feasibility of external cardiac massage. Several subsequent studies described the successful use of this method, first in children and then in adults, but it was not until this year (1960) that the technique achieved a sound medical basis (1). External pressure on the sternum at the rate of 60 per minute apparently provides enough blood flow to prevent anoxia, despite continued fibrillation or asystole. This allows time for precise electrocardiographic diagnosis, for the use of an external defibrillator or pacemaker as indicated, and for the formation of a plan of action. We have repeatedly obtained these results in dogs and plan to set up an arrhythmia center for humans. If its efficacy is confirmed, this technique will be taught to the general public. As a by-product, physicians may be called to treat many more patients with asystole or ventricular fibrillation. Thus it is essential that all physicians have an excellent understanding of the management of these problems.

This method will help to eliminate loss of composure as a cause of error on the part of the physician. He will now be able to walk casually to the stricken patient, even in the middle of a crowded dance floor, listen to the heart, and say with dignity, "Keep pumping, Jack, while I sit here and write out a plan of action."

In addition, this technique may help to prevent therapeutic mishaps, because fear of such mishaps often leads to administration of a drug in a dose too small to accomplish the desired result.

The patient who has suddenly become unconscious and is without pulse or heartbeat has asystole or ventricular fibrillation. Differential diagnosis is impossible unless auricular waves are present in the neck veins. Within a few minutes the brain cells die or the heart dilates, making external electrical reversion impossible. Immediate external cardiac massage is mandatory, along with mouth-to-mouth breathing. An open airway must be insured. Several forceful blows should be given to the chest while awaiting ancillary procedures. In one of our patients, prior to the development of pacemakers, asystole was corrected by this method more than 100 times during a period of eight hours. One of the periods of asystole lasted six minutes. The patient sat up following resumption of heart activity and asked why we had been pounding on his chest. The asystole could not be prevented by the use of atropine, intravenous epinephrine or Isuprel.

We lost the patient eventually because of our fatigue and bleeding, bruised hands. Autopsy demonstrated an apparently normal heart. In this case, the availability of a pacemaker might have been life-saving.

If the patient has been unconscious for more than three minutes before external massage is started, the heart is probably dilated and may not respond to external electrical stimulation, even though there has been a return of consciousness with external massage. The problems involved in a trial with a pacemaker are casual. However, defibrillatory shocks are flesh-searing and the opening of a chest in a conscious patient is not desirable. The options are to discontinue massage until the patient lapses into unconsciousness or to delay the procedures until an anesthetic can be administered.

Paroxysmal auricular tachycardia

The treatment of paroxysmal auricular tachycardia is urgent only when this arrhythmia complicates another medical disorder such as myocardial infarction, or when it occurs during surgery. Paroxysmal auricular tachycardia is treated by vagal stimulation alone or, in refractory cases, by vagal stimulation after the administration of digitalis in progressively larger amounts up to the digitalizing dose. The single best method of stimulating the vagus is by attempting to obtain an esophageal electrocardiogram for precise auricular evaluation. In 33 consecutive cases there was a reversion of rhythm before an electrocardiogram was obtained. The choice of a digitalis preparation is a matter of medical judgment regarding the immediate need for reversion of rhythm. If the attacks are frequent and disabling, they can be prevented by full digitalization followed by daily maintenance doses.

Auricular fibrillation

Auricular fibrillation is another cause for concern by both patient and physician. Clinically, there are two types of auricular fibrillation. The first type is paroxysmal, and usually occurs in apparently normal persons. The attacks are self-limiting, but they may be stopped with relatively small doses of quinidine. Digitalis does not slow the rate in the absence of cardiac failure. The second type is commonly associated with heart disease and failure. Digitalis slows the ventricular rate unless a complication such as thyrotoxicosis is present. Reversion to normal rhythm usually is not urgent, and it often occurs during a digitalization regimen, despite accepted opinions to the contrary.

The presence of these two types of fibrillation is well illustrated by the following case: A young man with severe mitral stenosis, auricular fibrillation and cardiac failure responded well to digitalis. Upon return from the operating room his heart was fibrillating with a ventricular rate of 70. Two days later he had a two-hour attack of very rapid paroxysmal auricular fibrillation, which then reverted to the previous status of fibrillation.

"Skillful neglect" is a good rule to follow in the treatment of paroxysmal auricular fibrillation or flutter in urgent situations, regardless of medical pressure. The attack usually ends spontaneously. Should the attack persist, small doses of

Rythmol[1] may be used. In several patients of our series the rhythm reverted from fibrillation or flutter to sinus rhythm within minutes after the intravenous administration of 100 mg. of Rhythmol (2). Patients with acquired heart disease are usually digitalized prior to surgery. The knowledge that the patient has received an adequate amount of digitalis is an invaluable contribution to the composure of the physician, should arrhythmias develop. Quinidine should not be used in these patients unless the arrhythmia has persisted for at least a week.

OBSERVATIONS ON THERAPY

Digitalis

Digitalis is the cornerstone of cardiac therapy; arrhythmias caused by overdosage or metabolic derangement can be avoided by adhering to the following rules:

1. After learning all there is to know about the specific actions involved, adopt one digitalis preparation for each purpose, *i.e.*, for rapid or moderately rapid parenteral use, for oral digitalization, and for maintenance. Adhere to this program consistently.

2. Always use a whole-leaf preparation for oral maintenance. This is practically dogma. "Whirling propellers" at the periphery of vision, an "icky" feeling, loss of appetite, or nausea are valuable guideposts, particularly when arrhythmia is present.

3. Do not restrict salt severely except when cases of advanced failure do not respond to simpler measures.

4. Give diuretics with caution and compensate for the loss of potassium. Be on the alert for the patient in whom diuresis does not occur as expected. One of the most dangerous latter-day developments has been the oral diuretic which drains off fluid but does not discriminate between the noxious "enemies" and necessary "friends."

5. Follow the patient closely. In hospital clinics the longest interval between visits is four weeks. Why should not this be true in private practice?

Quinidine

We have used quinidine for many years without trouble, adhering only to the dictum that large doses given to a patient receiving digitalis are apt to precipitate ventricular fibrillation. The following experiences have convinced us that the concern about the dangers of quinidine were well founded:

1. Some two years ago, we attempted to compare the effect of 100-mg. intravenous injections of Rythmol (previously proved safe) with the effect of injections of quinidine or procaine amide (Pronestyl).[2] One patient who tolerated Rythmol without trouble died after a comparable injection of quinidine.

2. In 3 patients treated with quinidine, thrombocytopenic purpura developed within two months.

[1] 2,6-bis(1-piperidylmethyl)-4-(a,a-dimethylbenzyl) phenol dihydrobromide.

[2] N′-(2-diethylaminoethyl)-para-aminobenzamide.

Procaine amide

This drug should be reserved for severe cases of ventricular tachycardia. It may be used intravenously for better control of hypotension. It is ineffective in some cases. Asystole is a danger when there is underlying A.V. node damage or the patient has been digitalized. Agranulocytosis has been observed in association with its use.

NEED FOR MORE EFFECTIVE ANTI-ARRHYTHMIA DRUGS

The foregoing facts are not discussed in order to condemn the use of these valuable drugs but to point out to the drug industry and the medical investigator the necessity of a continued search for more suitable compounds. This need is illustrated by the following case:

The patient was a 29-year-old white male attorney. Since the age of 15 he had suffered from increasingly frequent disabling attacks of paroxysmal tachycardia. Occasionally they could be aborted by vagal stimulation early in an attack when the rhythm was regular. When such attempts failed, the rhythm eventually became irregular and the tachycardia persisted for several hours. These episodes often were precipitated by the excitement of a courtroom trial having serious social and economic implications.

One day our technician obtained serial electrocardiograms during part of an attack. The basic slow rhythm showed WPW complexes (Fig. 1). Lead I of the initial tachycardia tracing is illustrated in Figure 2A. The ventricular rate was 220 per minute and the beat was regular. The QRS complexes were widened, and P waves were present. The auricular rate appeared to be slower than the ventricular rate. There was no relation between the P waves and the QRS complexes. This was interpreted as ventricular tachycardia. By the time Lead III was recorded, supraventricular tachycardia with a rate of 220 had developed. Leads I and II (Fig. 2B) of the next serial electrocardiogram are shown for purposes of comparison with the foregoing tracings. The arrhythmia was present throughout the recording of this 12-lead electrocardiogram. Lead V3 demonstrated electrical alternans not present in V2 or V4 (Fig. 2C). The supraventricular rhythm persisted for an undetermined period. Then the technician observed a change in the regularity of the feat, and obtained a third electrocardiogram. Lead I (Fig. 2D) was interpreted as rapid auricular fibrillation with a short period of ventricular tachycardia. Leads II (Fig. 2E) and III defied description. Auricular fibrillation with a ventricular rate of about 120 was present in AVR through AVL. In V1, a series of auricular P waves suggestive of flutter appeared (Fig. 2F), but the flutter immediately reverted to fibrillation (Fig. 2G).

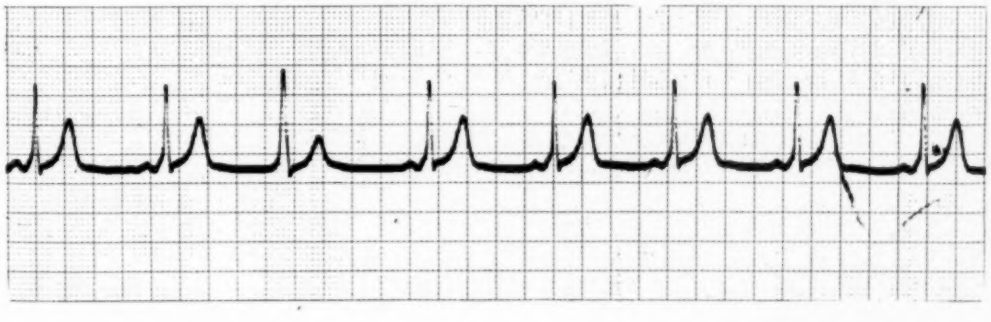

FIG. 1. Basic slow rhythm: WPW complexes with one nodal extrasystole.

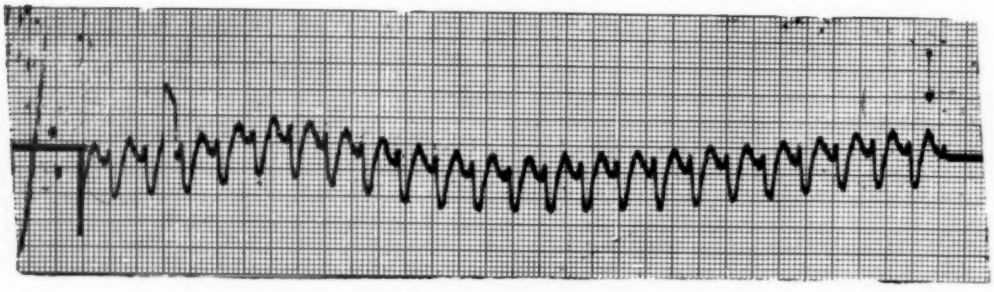

Fig. 2A - Lead I

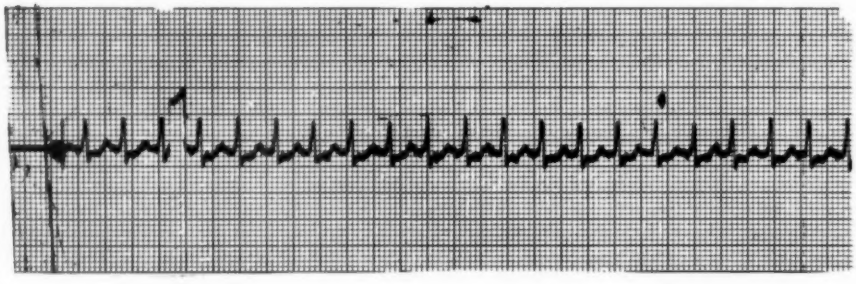

Fig. 2B - Lead I

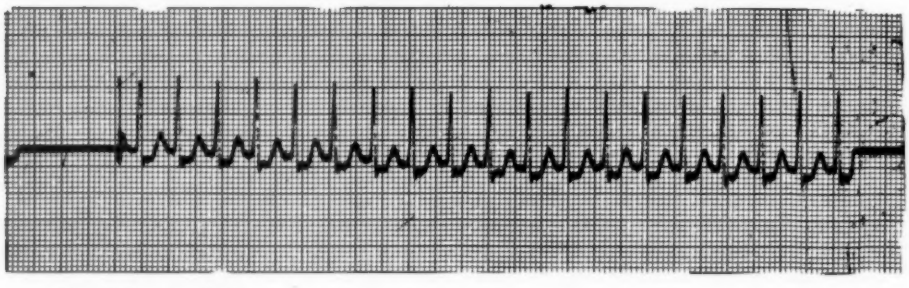

Fig. 2B - Lead II

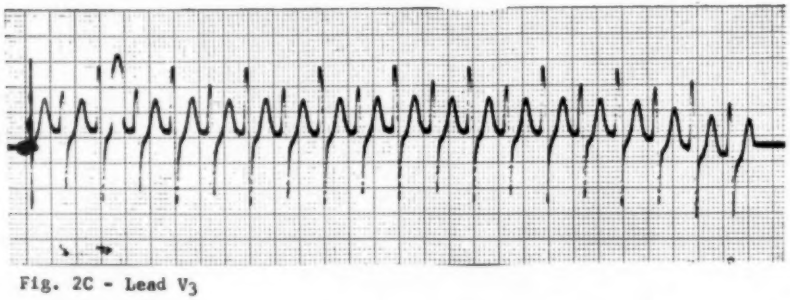

Fig. 2C - Lead V_3

FIG. 2. Serial electrocardiograms obtained during an episode of tachycardia (see text for a complete description).

2A—Lead I. Probable ventricular tachycardia.

2B—Leads I and II. Supraventricular tachycardia.

2C—Lead V_3. Electrical alternans.

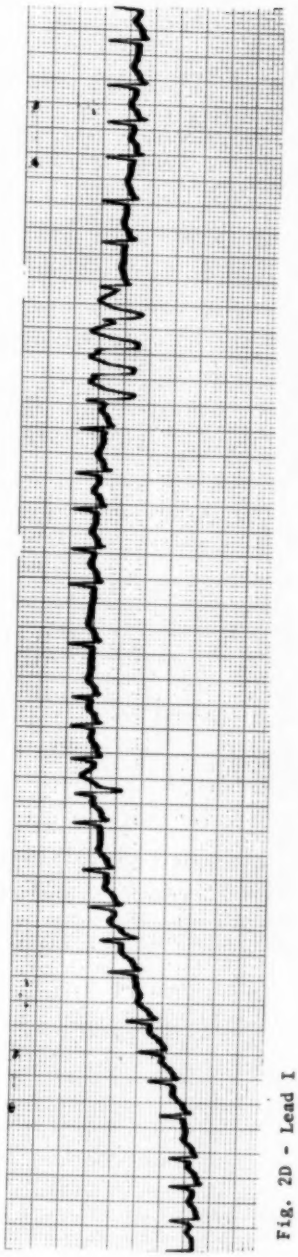

Fig. 2D - Lead I

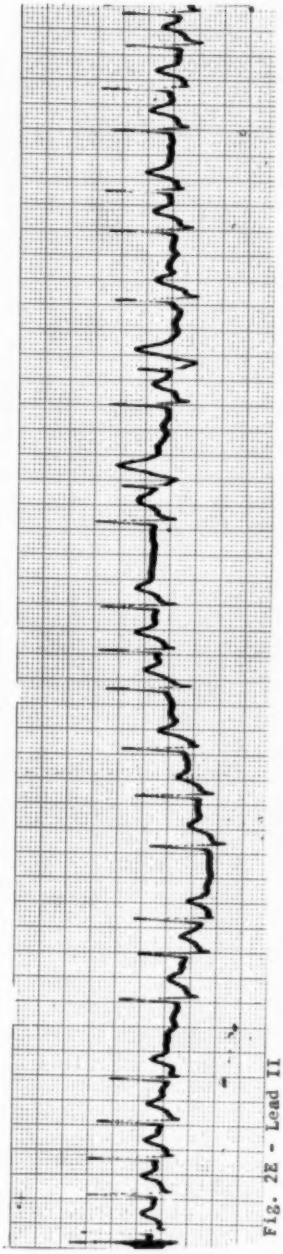

Fig. 2E - Lead II

2D—Lead I. Rapid auricular fibrillation with a short period of ventricular tachycardia or fibrillation.
2E—Lead II. The auricles and ventricles seem antagonistic.

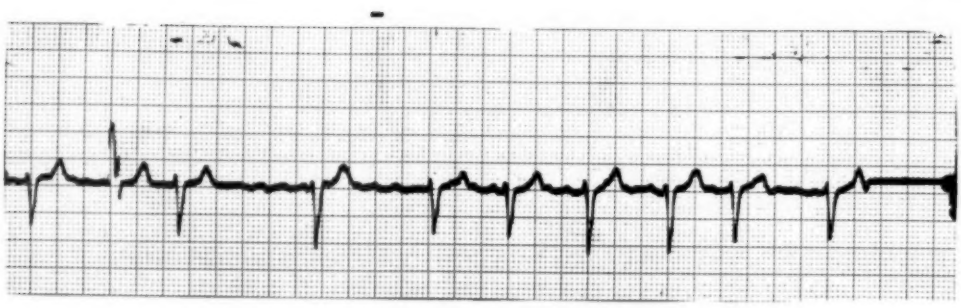

Fig. 2F - Lead V_1

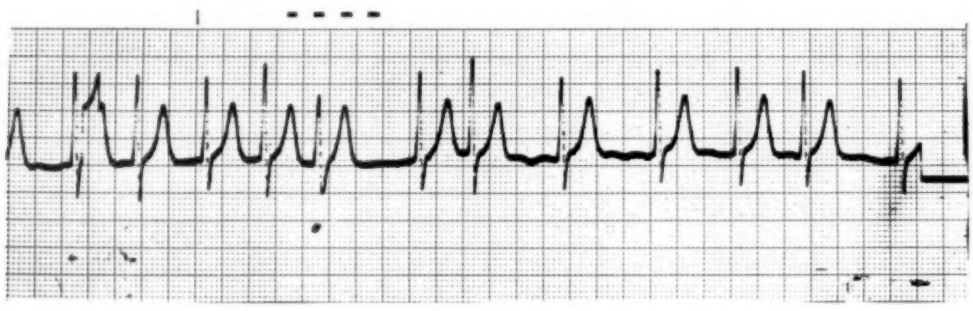

Fig. 2G - Lead V_4

2F—P waves suggest auricular flutter.
2G—Auricular fibrillation with slower ventricular rate.

The ventricular rate of 120 was compatible with ordinary activity, so the patient returned to his work. This was his usual procedure. He had come to our office only because of our repeated requests to allow us to make an electrocardiographic record during an attack. Digitalis therapy was tried, but the episodes of tachycardia became more frequent. Procaine amide was ineffective. Quinidine afforded complete relief from tachycardia and was considered satisfactory medication until the day the patient came in to our office looking like a walking blood spot, because of thrombocytopenic purpura. The purpura, fortunately, responded to treatment.

It is obvious that safer effective anti-arrhythmia drugs are needed. Perhaps Rythmol will prove to be one of them.

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SUMMARY OF THE PANEL DISCUSSION ON TREATMENT OF CARDIAC ARRHYTHMIAS

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There is a tremendous difference in the response to therapy of acute paroxysmal atrial tachycardia and chronic atrial fibrillation in the presence of heart disease. Whereas the acute attack will often disappear after an injection of morphine, sedation, or just a good night's sleep, chronic fibrillation presents a more difficult therapeutic problem. The usefulness of Ro 2-5803 as an anti-arrhythmic agent is impossible to evaluate on the basis of the material presented today. There would seem to be, however, some geographic differences in the pharmacology of this agent, in that it appears to be effective in ventricular arrhythmias in Philadelphia, but ineffective in atrial arrhythmias in Washington. It has been suggested that one reason for this ineffectiveness in atrial fibrillation is failure of the drug to be fully absorbed. Unfortunately, there is as yet no means of recording its concentration in the blood, and only recently has its absorption in tissue concentrates been determined by the use of isotopes.

A very important therapeutic problem, particularly in patients seen in hospitals and clinics, is that of digitalis-induced arrhythmias, a problem further augmented by the frequent use of benzothiadiazine diuretics with concomitant potassium loss. It should be emphasized that digitalis can induce all of the known arrhythmias, as well as arrhythmias not yet described.

It is generally agreed that there is need for more effective and less toxic anti-arrhythmic agents. Drugs such as Ro 2-5803 would appear to offer some promise, particularly in the area of ventricular arrhythmias. There is still reason for using quinidine and foxglove. However, we hope that Ro 2-5803 may herald similar drugs which will prove successful in this important therapeutic field.

Abstracts of Current Literature

CLINICAL PHARMACOLOGY OF VARIOUS TYPES OF FIBRINOLYTIC ENZYME PREPARATIONS.

Ambrus, J. L.; Ambrus, C. M.; Sokal, J. E.; Markus, G.; Back, N.; Stutzman, L.; Razis, D.; Ross, C. A.; Smith, B. H.; Rekate, A. C.; Collins, G. L.; Kline, D. L., and Fishman, J. B. *Am. J. Cardiol.* **6:** 462 (Aug.) 1960.

One hundred and ninety-six patients were treated with various types of fibrinolytic enzyme preparations. Following 538 intravenous and/or intra-arterial infusions, hemorrhage occurred in 12 cases, and pulmonary embolism in 2. Pyrogenic side-effects were seen commonly with earlier preparations but only 4 times in 385 treatments with newer, more purified preparations. With four-hour to eight-hour infusions, a decrease in factors of the blood clotting system was never of sufficient magnitude to be of clinical significance. Rapid intravenous injection resulted in more pronounced changes. Factors most often affected were prothrombin, factor V, factor VII, and fibrinogen. Retreatment with streptokinase or streptokinase-activated plasmin three weeks after an initial course of therapy resulted in anaphylactoid reactions in 2 of 3 cases. Retreatment with urokinase-activated plasmin caused no side-effects and did not result in decreased therapeutic activity in 12 cases. Sixty-two cases of thrombophlebitis or thrombosis of the large veins (chiefly complications of neoplastic diseases in elderly patients) of less than five days' standing were treated with streptokinase, urokinase- or chloroform-activated plasmin, streptokinase or urokinase, alone or in combination with anticoagulants; 28 (45 per cent) returned to normal, 20 (32 per cent) improved in less than five days, 6 (10 per cent) did not improve, and 1 patient died of pulmonary embolism. All preparations used appeared to be therapeutically active. The objectives and methods of study precluded the use of a matched control group of patients on a randomized double-blind basis. Nevertheless, therapeutic results in the groups of patients treated with fibrinolysin were superior to those in the untreated group or groups treated with anticoagulants. (From authors' summary.)

DIAGNOSIS OF ANGINA PECTORIS.

Andrus, E. C. *Circulation* **22:** 979 (Nov.) 1960.

The best diagnostic procedure is a careful history, with special attention to the patient's account of the distress, its distribution, and the circumstances under which it appears. The pain, characteristically, is squeezing, choking, pressing, aching or burning. It increases gradually to maximal intensity, persists for a few minutes, and then usually rapidly subsides. The pain typically begins in the midline behind the sternum, usually in its upper two-thirds. It spreads symmetrically to areas near the sternum and commonly extends over the upper pectoral region to the neck, to the front of the shoulders, and down the medial aspect of the arms to the wrists and hands, particularly on the ulnar side. Anginal pain should not be confused with the pain of esophageal spasm or disease, which tends to wax and wane, to penetrate to the midline in back, and to be influenced by swallowing. The left side of the body usually is affected more than the right in angina pectoris. The pain also may appear in the hands, wrists and arms. Infrequently, it spreads to the jaw, teeth, face or suprascapular area. Angina pectoris appears under the stress of exertion, anger, "aggravation" or excitement, the effect of any of these being intensified after a meal. The relationship between inciting factor and occurrence of pain gives a clue in differentiating angina pectoris from pain that occurs in acute pericarditis, anxiety, neurocirculatory asthenia and periarthritis, for example. The pain of angina pectoris decubitus which occurs at the beginning of a meal is more difficult to distinguish. When the history suggests angina pectoris, some confirmation may be found in discovering conditions like hypertension, cardiac hypertrophy, aortic stenosis or regurgitation that contribute to the development of coronary insufficiency. In

angina, the blood pressure usually rises. Transient signs of left ventricular failure may be detected and frequent extrasystoles or other arrhythmia may appear. An electrocardiogram at rest may be helpful when it indicates prior myocardial damage. The diagnosis, however, usually can be made clinically. If an electrocardiogram is to be made, it is best to record it during an attack. When this is not possible, a stress test may be used, which may provoke the characteristic attack or engender changes in the electrocardiogram. Its purpose is to disclose evidence of relative deficiency of myocardial blood supply, the validity of the results being dependent upon the ability of the test to distinguish abnormalities in the electrocardiogram from variations that appear after stress in the absence of significant disease. In interpreting the results of stress tests, the following changes, appearing after standard exercise, are taken to indicate coronary insufficiency: 1) S-T deviation of 1.5 mm. or more with a flattened or downward-sloping S-T segment in the limb leads or lateral chest levels (over the left ventricle); 2) inverted or diphasic T wave in leads I or II or lateral chest leads; and 3) the development of bundle-branch block or the appearance of frequent extrasystoles. Ballistocardiography as a means of detecting coronary artery disease or predicting its consequences is in an evolutionary stage. The ballistocardiogram can provide additional data regarding the likelihood of coronary disease if the findings are abnormal at rest or after exercise or smoking in a patient below age 40, or if the record deteriorates during an attack of pain.

SURGICAL CONSIDERATIONS OF OCCLUSIVE DISEASE OF THE GREAT VESSELS ARISING FROM THE AORTIC ARCH.

DeBakey, M. E.; Crawford, E. S.; Cooley, D. A.; Morris, G. C., Jr., and Henly, W. S. Thirty-third Scientific Session, American Heart Association, October, 1960; (abstract) *Circulation* **22:** 738 (Oct.) 1960, Part 2.

Thrombo-obliterative disease of the great vessels arising from the aortic arch is a clinical entity sometimes called Takayasu's disease, aortic arch syndrome, pulseless disease, reverse coarctation, or Martorell's syndrome. These terminologic variations along with certain reported concepts of the occlusive process have caused confusion regarding the nature of the disease process. Some proposed concepts of the pathogenesis of the disease preclude application of effective surgical treatment to restore normal circulation. Observations are reported from analysis of 50 cases using surgical treatment to restore normal circulation. The study supports the concept of the segmental nature of the occlusive process and its tendency to assume certain well defined patterns despite considerable variation in its pathologic features. Although the occlusive process may be extensive and the vessels may be involved in an inflammatory process probably incited by superimposed thrombosis, the underlying etiologic factor in most cases appears to be atherosclerosis. Clinical manifestations, including age and sex incidence, may be correlated with certain pathologic features of the disease. It also is significant that some patients have associated segmental occlusive disease in other parts of the major arterial tree, emphasizing the emerging clinical patterns of multiple segmental atherosclerotic occlusive disease. Results of surgical treatment were gratifying, and restoration of normal circulation in the distal arterial bed was achieved in all cases, including those associated with other occlusive lesions. Application of several surgical procedures, singly or combined in accordance with various patterns of occlusion, was studied.

LONG-TERM OBSERVATIONS OF INTERMITTENT HEPARIN THERAPY FOR THE PREVENTION OF CORONARY ATHEROSCLEROSIS.

Engelberg, H., and Kuhn, R. Thirty-third Scientific Session, American Heart Association, October, 1960; (abstract) *Circulation* **22:** 745 (Oct.) 1960, Part 2.

During the past nine years, 66 private patients with previous myocardial infarction have received heparin therapy for a prolonged period. Concentrated aqueous heparin was given subcutaneously in doses of 200 mg. twice weekly, three times a week in a few instances.

There were 3,912 months of therapy, or an average of 59.3 months per patient. During this time 10 patients died—an over-all mortality of 15.2 per cent, and a mortality rate of 3.1 per cent per year. There were no hemorrhagic deaths. Although a strict control group was not followed during the entire period, the mortality rate of 3.1 per cent indicates a 70 to 75 per cent reduction in anticipated mortality. This is based on an observed mortality rate of 11.5 per cent per year in a control group which was followed for two years. The low incidence of deaths in the heparin group is particularly significant since many of the patients had had several previous infarcts, had not responded to dietary measures by a lowering of the serum lipid level, or had experienced recurrence of infarction while receiving oral anticoagulant therapy. These results demonstrate that intermittent heparin therapy is effective and feasible in the prophylaxis of coronary atherosclerotic disease.

THE USE OF LONG-ACTING QUINIDINE GLUCONATE IN THE MANAGEMENT OF ATRIAL FIBRILLATION.

Greif, E., and Scheuer, J. *J. Mt. Sinai Hosp.* **27:** 612 (Nov.-Dec.) 1960.

In normal subjects, the mean serum quinidine level after the administration of 1 Gm. of quinidine base as quinidine sulfate reached a peak of 6 mg. per liter within three hours and fell to less than 1 mg. per liter in twenty-four hours. With quinidine gluconate, the level ascended at a slower rate, reached 4 mg. per liter after three hours, and reached a peak of 4.5 mg. per liter after five and a half hours. The level then fell to less than 1 mg. per liter in twenty-four hours. At twelve hours, the level was significantly higher with the long-acting preparation. In 8 patients with established atrial fibrillation the condition was converted to sinus rhythm with quinidine sulfate. Long-acting quinidine gluconate then was administered for maintenance in a dosage of 0.6 Gm. twice daily except in 1 patient who received this dose three times in a day. The minimal serum quinidine level, determined twelve hours after the evening dose of quinidine gluconate and before the morning dose, varied between 1.75 and 5 mg. per liter. No side-actions occurred during maintenance therapy. In 2 patients with paroxysmal atrial fibrillation severe gastro-intestinal symptoms and weakness forced discontinuation of both quinidine sulfate and gluconate. In 1 patient with paroxysmal atrial fibrillation, recurrences were prevented with two doses of 0.45 Gm. of quinidine gluconate daily. In 1 other patient it was necessary to give 0.6 Gm. of quinidine sulfate at 9 a.m. and 3 p.m. and a single dose of 0.6 Gm. of quinidine gluconate at night, in order to prevent attacks. This patient had not been able to tolerate 4 doses daily of quinidine sulfate because of nausea and diarrhea. It is concluded that quinidine gluconate is effective for maintenance of sinus rhythm in patients with previously established atrial fibrillation, and for the prevention of recurrent atrial fibrillation.

URINE SERUM GLUTAMIC OXALACETIC TRANSAMINASE ACTIVITY IN ACUTE MYOCARDIAL INFARCTION.

Kalmansohn, R. B., and Kalmansohn, R. W. Thirty-third Scientific Session, American Heart Association, October, 1960; (abstract) *Circulation* **22:** 769 (Oct.) 1960, Part 2.

An attempt was made to establish the method and normal levels for the determination of urinary glutamic oxalacetic transaminase (UGOT) activity and to evaluate these levels in patients with acute myocardial infarction. UGOT determinations were run on 39 controls with no evidence of acute disease; only 1 value was over 9 units (Karmen), the average value being between 4 and 5 units. Accordingly, it was felt that any level over 9 units could be considered abnormal. The urinary pH and specific gravity did not appear to influence the result. However, the UGOT activity gradually disappeared after thirty minutes of standing at room temperature or in a refrigerator. Daily UGOT determinations were made in 15 consecutive patients with acute myocardial infarction proven by electrocardiograms and serum indices of myocardial necroses. All 15 patients had elevated UGOT levels ranging from 17 to 46 units and persisting for a minimum of three days. The height of the UGOT levels was

not particularly correlated with the height of the SGOT levels, but the levels in both serum and urine remained elevated about the same length of time. This is an additional method of evaluating myocardial necrosis. The assay is easy to perform and does not require multiple venipunctures.

RENAL MEDULLARY NECROSIS.

Lauler, D. P.; Schreiner, G. E., and David. A. *Am. J. Med.* **29:** 132 (July) 1960.

Six cases are presented. The literature on renal medullary necrosis is reviewed, and 250 cases are analyzed. This is an ischemic necrosis involving the renal medulla. In the absence of localizing obstructive or vascular factors, it generally is bilateral and most often associated with urinary-tract infections. "Renal medullary necrosis" is the preferred term although necrotizing papillitis, papillary necrosis, and necrotizing pyelonephritis have been used. The disease is more common in older age groups, more women than men being affected. Various theories of pathogenesis have been proposed. Infection is agreed to be the cause. The authors believe that renal medullary necrosis is a form of pyelonephritis which is more devastating than uncomplicated pyelonephritis because its natural course is altered by associated disease states, primary among which are the diabetes, pre-existing renal disease, urinary-tract obstruction, and nephrosclerosis. They view it as generated by an uncontrolled infection, and abetted by local vascular tissue factors and by defective resistance on the part of the host. The chief clinical characteristics are a urinary-tract infection superimposed on diminishing renal function, especially in persons over the age of 40 years. The infection frequently will be a fulminating pyelonephritis. The diagnosis should be suspected in a patient with a sudden toxic course following genito-urinary tract instrumentation or surgery, especially if there is pre-existing renal disease. It also should be suspected in diabetic patients with disproportionate acidosis or in those who are in coma and respond poorly to treatment, or who respond to therapy but have persistent progressive azotemia. The presenting signs will be those referable to the urinary tract, such as dysuria and lumbar pain. Chills and fever are common. There usually will be a moderate leukocytosis with anemia and an elevated sedimentation rate. Bacteriuria, pyuria, hematuria, albuminuria, and cylindruria will be present sometime in the course of the disease. Percutaneous renal needle biopsy may aid in diagnosis. Retrograde pyelography may be dangerous, and intravenous pyelography should be undertaken only with great caution. The principal problem in differential diagnosis is distinguishing acute tubular necrosis and renal cortical necrosis. Eradication of infection is the basis of treatment. Antibiotic therapy should be undertaken, with sensitivity tests for the infecting micro-organisms. All inciting factors, and especially urethral catheterization, should be avoided. Any obstructive element must be evaluated for surgical removal. The prognosis will depend upon 1) the delay in diagnosis in relation to onset of the disease, 2) the therapy (including correction of infection and/or the surgical correction of known predisposing factors), and 3) the progress of any predisposing or associated disease state. The onset may be abrupt, with fulminating acute renal failure. It may be insidious when there is an underlying disease state such as a urinary-tract obstruction. In the latter instance, the diagnosis may be delayed until progressive involvement results in azotemia and uremia associated with sepsis. The disease is compatible with survival, as indicated by the review of cases and the one case reported, but no survival rate can be given because in the past the disease was usually recognized by postmortem findings.

ZUR KENNTNIS DER PACHYMENINGITIS HAEMORRHAGICA INTERNA UND DES PACHYMENINGITISCHEN HÄMATOMS DER DURA MATER (INTERNAL HEMORRHAGIC PACHYMENINGITIS, AND PACHYMENINGITIS HEMATOMA OF THE DURA MATER).

Link, K. *Monatschr. f. Unfallheilk.* **92:** (7); 194, 1958; through Excerpta med. (Gerontol. & Geriatrics) **3:** 153 (March) 1960.

A distinction must be made between post-traumatic subdural hematoma and internal hemorrhagic pachymeningitis. Seven hundred and thirty-six cases of the latter condition

are considered. On the basis of the anatomic and histologic findings, 4 varieties are distinguished—the evolutive, florid, saccular, and cicatricial. Internal hemorrhagic pachymeningitis may present a tumor-like condition, with or without compression. Localizations: bilateral in 36 cases, on the convexity in 43 cases, at the base in 2 cases, and simultaneously on the convexity and at the base in 16 cases. Hematomata were found only on the convexity. Among all these cases there were only 10 instances of trauma. Internal hemorrhagic pachymeningitis may accompany cardiac disorders, pulmonary disturbances or cerebral, hepatic or renal disease, or it may be due to senility. The disease is a specific disorder of the dura mater; its etiology is not yet completely known. The condition often originates from circulatory disturbances, endogenous intoxications, or insufficiency of the right or left heart; associated traumata have also been found. The existence of a primary form of internal hemorrhagic pachymeningitis is improbable. A review is given of the processes and of the genesis of the lesions. The maximal age for these disturbances lies between 60 and 80 years. The condition progresses in discrete stages. Treatment consists in puncture or extirpation of the hematic sac. The result depends upon the stage of the causative process. If a normal dura mater is found, the condition is unquestionably one of post-traumatic hematoma. Internal hemorrhagic pachymeningitis must be distinguished from subdural hemorrhage, which is characterized by processes of reabsorption, organization and cicatrization. Pachymeningitis presupposes a pathologic condition of the dura mater.

HYPERTENSION AND CEREBROVASCULAR DISEASE.

Marshall, J. *Lancet* **2:** 881 (Oct. 22) 1960.

The blood pressures of 134 patients with a history of cerebral infarction showed a bimodal distribution. Among those patients over age 60 years, this distribution was due to a group with hypertension that was unrelated to the age at death of their parents. Among patients aged 60 years and under, bimodal distribution was confined to those whose parents (one or both) died before the age of 65. Thus an hereditary factor must have been operative in the second group but not in the first. This emphasizes the importance in studies of the role of hypertension in cerebrovascular disease of not treating all patients with hypertension as a uniform group. This study also leads to the conclusion that the level of blood pressure cannot be considered a feature distributed continuously throughout the population but that there are different groups, the recognition and study of which will aid in understanding hypertension and its relation to cerebrovascular disease. The approach to an understanding of cerebrovascular disease must not be limited to distinguishing in life and after death between embolic infarction, nonembolic infarction and hemorrhage, but must take into account dynamic factors in the patients' life histories which may give clues to the etiology and lead to better means of management of cerebrovascular disease.

VAGINAL SMEARS IN WOMEN PAST 40 YEARS OF AGE, WITH EMPHASIS ON THEIR REMAINING HORMONAL ACTIVITY.

Masukawa, T. *Obst. & Gynec.* **16:** 407 (Oct.) 1960.

The hormonal status of 262 postmenopausal women selected from a group of 2,103 patients was evaluated by the maturation index method using vaginal smears. Intermediate cells predominated in all age groups from 40 years to 70 and more, and in all postmenopausal years grouped from 1–10 to 31+. Superficial cells declined gradually, whereas parabasal cells increased with age. Parabasal cells gradually increased with the number of years after the menopause, and an abrupt decrease of superficial cells occurred approximately ten years after the menopause. The only change of statistical significance was that of the superficial and parabasal cells between the first and second ten-year postmenopausal groups. Using superficial cells as the criterion of estrogenic activity, only 22 per cent of the total group of patients showed no evidence of estrogenic activity. Estrogenic activity was present in 90, 76, 70 and 77 per cent of patients in the 1–10, 11–20, 21–30 and 31+ postmenopausal

years, respectively. When the degree of atrophy was judged by the numbers of parabasal cells in the vaginal pool smears, the percentage of all degrees of atrophy present in the various postmenopausal groups was 24,50,55 and 76 per cent, respectively. A need exists for an objective expression of the normal postmenopausal smear pattern. Such studies should serve as a basis for judging what role, if any, persistent estrogenic function may play in carcinoma of the breast, for the evaluation of ablation and hormonal therapy using the smear technic, for investigation of the possibility of using the vaginal smear for prognostic purposes, and for the detection of endocrinologically active disorders such as hormone-producing tumors.

HAMMAN-RICH SYNDROME (DIFFUSE INTERSTITIAL PULMONARY FIBROSIS).
Maxwell, W. M., and Campbell, P. E. *M. J. Australia* **1:** 616 (Apr. 16) 1960.

The Hamman-Rich syndrome is not as rare as once thought. An increasing number of cases has been reported in the last fifteen years. These have emphasized the subacute and chronic forms which are more common than the acute form originally described. Diagnosis during life has been facilitated by biopsy of the lung and by pulmonary function tests. The cause of the disease is unknown. It may be the sequel of the action of several agents, each producing inflammatory edema of the alveolar walls. It is characterized pathologically by increasing and widespread interstitial pulmonary fibrosis of slow but occasionally rapid progress. The clinical features are progressive dyspnea with cyanosis, clubbing of the digits, and diffuse basal rales. The pulmonary physiology indicates fibrosis and alveolar-capillary block. Roentgenographic examination shows widespread fibrosis. The electrocardiogram typically shows right ventricular hypertrophy. The syndrome occurs among middle-aged persons, both sexes being equally affected. Chronic unresolved pneumonia is the most difficult problem in differential diagnosis. The only effective treatment is cortisone and its derivatives, which must be given early in the disease in order to be successful. Nine cases are reported, 8 of which occurred during the last four years.

PROGNOSIS AND ANTICOAGULANT PROPHYLAXIS AFTER CORONARY OCCLUSION.
McMichael, J., and Parry, E. H. O. *Lancet* **2:** 991 (Nov. 5) 1960.

The survival of patients after recovery from myocardial infarction, and factors that influence prognosis, were studied in a reported series of patients. Data on more than 5,000 patients are in agreement that the prospect of five-year survival in persons under the age of 60 years is 65 to 70 per cent. The chance of survival is higher among younger persons who have made a good recovery, but grows less with increasing age in persons with extensive lesions and with complicating conditions like hypertension and diabetes. The survival rates in published studies have ranged from 80 per cent among a group of physicians to 32 per cent in a study of elderly persons. All of the evidence indicates that myocardial infarction often may be followed by long survival. In assessing reports on anticoagulant prophylaxis, the authors are critical of the controls used because the survival prognoses in these cases often were at or below the lower extremes for untreated patients, and the treated patients fared no better than those with survival prospects in the upper range. As yet, evidence is inadequate that long-term use of anticoagulants prevents recurrence, or reduces mortality, after the acute phase of infarction. Long-term anticoagulant prophylaxis as carried out today shows no evidence of improving life expectancy when compared with the prognosis in the large group of "untreated" patients. Most of the benefits reported in careful studies have occurred in the first few months when the patients were recovering from the acute phase. If a drug is to prevent arterial thrombosis, its action should not cease after a few months. It may even be that the early benefits are related to the healing phase of the actual infarction. Thus far, they have been related to the efficacy of the drug in limiting venous thrombosis and preventing pulmonary embolism. It is pointed out that the mechanisms of venous and arterial thrombosis differ. Observations like the development of arterial occlusion in hemophilic patients, and the almost equal frequency of formation of mural thrombi over

infarcts in patients receiving and not receiving anticoagulants, raises doubts as to the usefulness of anticoagulants in preventing local thromboses on damaged arterial intima. Any possible benefit from anticoagulant therapy must be weighed against the risk of hemorrhage mentioned in many reports. Not only may anticoagulants not avert occlusion but there is a risk of thrombosis in the period after the drugs are stopped. When they are used in the acute phase of a myocardial infarction, their administration should be tapered off over a period of three to four weeks. Other reasons that anticoagulants may not be of benefit lie in the fact that factors other than thrombosis play a part in the production of myocardial infarction—thickening of atheromatous plaques, subintimal hemorrhage, or sudden reductions in blood pressure reducing perfusion of critically narrowed coronary vessels. Also, recurrent thrombosis may account for a little more than half of the ultimate death rate for patients who have recovered from a cardiac infarction.

THE CLINICAL PATTERN IN CERTAIN TYPES OF OCCLUSIVE CEREBROVASCULAR DISEASE.

Millikan, C. H.; Siekert, R. G., and Whisnant, J. P. *Circulation* **22:** 1002 (Nov.) 1960.

A clinical classification has been adopted for cases of occlusive cerebrovascular disease, as follows: 1) *incipient or impending stroke*, 2) *advancing stroke*, and 3) *completed stroke*. Two types of intermittent focal cerebrovascular insufficiency make up the first category: *intermittent insufficiency of the vertebral-basilar system*, and *intermittent insufficiency of the carotid system*. The symptoms and signs of *insufficiency of the vertebral-basilar system* include episodes, sudden in onset and generally of five to twenty minutes' duration, characterized by the following combinations: monoparesis, hemiparesis, or paralysis occasionally shifting from side to side and potentially involving all or any combination of extremities; sensory defects commonly affecting both sides of the body; bilateral defects throughout the visual fields; diplopia; vertigo; dysarthria; dysphagia; and alteration of consciousness. Not all of these will be present, but diagnosis cannot be made with certainty unless two or more are present. Episodic vertigo is extremely common. Bilateral homonymous hemianopsia is almost pathognomonic. In *insufficiency of the carotid system*, there may be a history of transient episodes of weakness or numbness limited to one side of the body; aphasia, if the dominant hemisphere is involved; or impaired vision in the eye on the side of the lesion. Physical signs in some instances are diminished pulsation in the carotid artery on the involved side; relative hypotension in the retinal artery on the involved side (ophthalmodynometer); and bruit over the carotid artery or eye on the involved side. Weakness is most commonly present, but all or only a portion of these symptoms and signs may be present. Only in cases of multiple stenosis, occlusion of one vessel and stenosis of another, or abnormal anatomic relationships are diplopia, bilateral homonymous hemianopsia, dysphagia, vertigo and bilateral impairment of motor or sensory function a part of the clinical picture of insufficiency of the carotid system. The primary or static defect in attacks of intermittent focal cerebrovascular insufficiency is atherosclerosis. The mechanisms by which attacks are produced include transient hypotension, polycythemia, external compression or kinking, anemia, multiple emboli, smoking, vasospasm and beginning thrombosis. The correction of any of these may relieve attacks. In the second major category—*progressing or advancing stroke*—ischemia is of such duration and severity that relatively permanent to severe damage is produced. These attacks may begin like those of carotid or vertebral-basilar insufficiency but they do not abate in a few minutes. They grow worse until the neurologic deficit may be severe and extensive when significant infarction has taken place. When infarction due to thrombosis is the cause, worsening may continue stepwise for hours. When an infarct occurs secondary to embolism, the development is rapid, and accomplished within seconds or minutes. Progressing strokes due to thrombosis also are divided into those of the carotid and vertebral-basilar systems. In both there will be: 1) a history of antecedent or warning attacks of intermittent insufficiency, 2) steplike progression over many minutes or hours, 3)

a rather minimal amount of pain in the head, particularly when in the carotid system, 4) preservation of consciousness generally, and 5) clear cerebrospinal fluids. Evidence of atherosclerosis in the heart, kidneys or extremities may be present. In *thrombosis of the carotid system*, besides warning episodes, there will be symptoms indicating a focal lesion in one hemisphere, progressing for hours. The neurologic symptoms and signs include monoparesis to hemiplegia; hemianesthesia; homonymous visual-field defect or impaired vision in the eye on the side of the lesion; and aphasia (dominant hemisphere). As in carotid intermittent insufficiency, physical signs referable to the patency of the appropriate carotid system may be suggestive. Phenomena observed in *thrombosis of the vertebral-basilar system*, besides antecedent transient episodes in 75 per cent of cases, include a neurologic syndrome developing during hours or a few days, with progression frequently in stepwise fashion; a neurologic deficit, including combinations of bilateral visual-field defects; nystagmus; impaired ocular rotations, particularly internuclear ophthalmoplegia; all or any combination of limbs exhibiting an upper motor neuron type of weakness; sensory changes, also variable in distribution; dysarthria; dysphagia; and impairment of consciousness. Certain combinations of impairment of bilateral visual fields, nystagmus, dysphagia, and weakness of bilateral extremities with altered reflexes are characteristic when correlated with the history. Two special-vessel subdivisions of progressing stroke within the vertebral-basilar system are *occlusion of the internal auditory artery* and *occlusion of the posterior inferior cerebellar artery*. When the *internal auditory artery is occluded*, the patient complains of sudden loss of hearing in the ear and has severe nausea and vomiting. Vertigo is extreme, but the patient gradually improves. The hearing loss is permanent. The phenomena observed upon *occlusion of the posterior inferior cerebellar artery* include vertigo, nausea, and vomiting; dysarthria; dysphagia; ipsilateral palatal palsy; ipsilateral Horner's syndrome; ipsilateral involvement of pain and thermal sensation on the face; contralateral involvement of pain and thermal sensations on limbs and trunk; and ipsilateral ataxia of the limbs. Neither of these two special-vessel subdivisions is characterized by long progression or recurrence. Another type of stroke is that caused by *embolism*. Important phenomena in its diagnosis are: sudden development of signs of a local brain lesion (within seconds or a few minutes); absence of prodromal manifestations in most cases; relative preservation of consciousness; existence of a source of emboli usually in the heart (either cardiac arrhythmia or infarction); evidence of recent embolism in other organs, that is, spleen, kidney, extremities, intestines or lungs; or in several regions of the brain in different cerebrovascular territories. Precise differential diagnosis may make possible early treatment, or assist in preventing future emboli to the brain and other organs. Progressing stroke also includes *hypertensive intracerebral hemorrhage*. Symptoms and signs of value in diagnosis are grossly bloody cerebrospinal fluid; hypertension; rapid evolution of hemiplegia and other phenomena over minutes or hours; onset generally during activity; headache (if the patient is sufficiently conscious to report his symptoms). Blood in the cerebrospinal fluid, present in 75 to 85 per cent of patients, is the primary sign. The development of neurologic phenomena usually occurs within minutes to hours and is smooth and without the steplike progress common to infarction. *Acute subarachnoid hemorrhage*, usually due to rupture of an intracranial aneurysm, must be considered in the differential diagnosis of a progressing stroke. The clinical phenomena produced by this condition are: sudden onset of severe headache; a stiff neck on forward bending; grossly bloody cerebrospinal fluid; an often relatively transitory disturbance of consciousness; and subhyaloid (preretinal) hemorrhages. A *completed stroke* means that the thrombosis or hemorrhage is no longer extending beyond anatomic confines and that infarction or other damage has reached maximal involvement for the stroke. The clinical syndrome no longer progresses but remains static, or improvement begins. The same principles of diagnosis apply as for the subcategories already mentioned. The clinician must rely upon observation and assessment to determine when the stroke is complete. In thrombosis in the vertebral-basilar system, completion is difficult to assess, since there may be no progression for hours or a day or two. In the carotid system, lack of progression for a few hours usually indicates that a stroke is complete. Improvement may then begin. Improvement is less no-

ticeable in intracerebral hemorrhage. Swiftness of onset and absence of stepwise progression make determination of completion of cerebral embolism fairly easy. Arteriography is needed in occlusive cerebrovascular disease only in the case of difficult diagnostic problems. It provides useful information in impending stroke, but serves little purpose in completed strokes. Its use may be dangerous in advancing strokes.

CONFUSION IN THE ELDERLY. SOME COMMON REMEDIABLE CAUSES.

Nobbs, K. L. G. *Lancet* **2:** 888 (Oct. 22) 1960.

Among common reasons for reversible mental confusion in elderly persons are blocked bowels, anemia, dehydration, and bronchopneumonia. Digital examination of the rectum will aid in diagnosing the first of these. The onset of the others is insidious. Mental confusion will disappear upon proper therapy of each of these conditions. Conditions causing confusion in the elderly and reported by other authors include cerebral disease, heart failure, pulmonary disease, uremia, anemia, hepatic failure, avitaminosis, endocrine disorders, cancer, injuries, and miscellaneous infections. Some drugs also may account for these confused states.

HYDROCHLOROTHIAZIDE USED ALONE IN CONGESTIVE HEART FAILURE AND IN COMBINATION WITH PREDNISONE AND OTHER DIURETICS IN CIRRHOSIS AND NEPHROSIS.

Porter, G. A., and David, N. A. *Am. J. M. Sc.* **240:** 417 (Oct.) 1960.

Hydrochlorothiazide was used as a diuretic in 20 hospitalized patients, 11 of whom had congestive heart failure, 8 cirrhosis, and 1 nephrosis. All patients were subjected to an initial three-day "control" stabilization period in order to offset the influence of such variables as bed rest, digitalization and salt-free diet on their subsequent response to diuretics. Daily measurements of body weight, blood pressure and urinary volume and electrolyte excretions were made. Serum electrolytes and bicarbonate were measured daily during the initial three-day "control" period and twice weekly during the therapy period. Blood urea nitrogen determinations were made weekly. Treatment was started with 50 mg. of hydrochlorothiazide orally, given three times daily after meals. Of the 11 patients with congestive heart failure, one was given this dosage plus an additional 75 mg. at bed time, and another was given this additional amount on the eighth day of trial. Duration of hydrochlorothiazide administration averaged thirteen and a half days (range five to forty days). Evaluation of diuretic response was based on changes in the body weight and urinary sodium excretion. In the patients with congestive heart failure, the response to hydrochlorothiazide was excellent in 5, good in 4, and fair in 2. Four of the cirrhotic patients and the 1 nephrotic patient failed to respond satisfactorily to initial use of hydrochlorothiazide. Consequently, other diuretics were added in an attempt to treat these patients adequately. With the concomitant use of hydrochlorothiazide and prednisone, 3 of these 5 patients responded satisfactorily. The remaining 2 proved refractory to the other forms of therapy such as combinations of hydrochlorothiazide and meralluride, meralluride and "chloride loading" and alternating daily therapy with hydrochlorothiazide or acetazolamide. Case reports on the 2 cirrhotic patients with ascites are presented, with charts showing the urinary responses and changes in serum electrolyte levels for each procedure tried. The results indicate that combined steroid-diuretic therapy is best reserved for those patients who are unresponsive to conventional forms of treatment. On the other hand, when allowance is made for the study method used (employment of an initial three-day stabilization period), the results obtained with hydrochlorothiazide in patients with congestive heart failure compare favorably with the results of other workers as to the efficacy of this new diuretic agent. (From authors' summary.)

PERIOSTEAL CHEST WALL PAIN AS PART OF THE POST-MYOCARDIAL INFARCTION SYNDROME.

Roesler, H. *Am. J. M. Sc.* **240:** 407 (Oct.) 1960.

Acute chest wall pain occurred in 2 patients approximately six and three weeks, respectively, after typical myocardial infarction. The pain was extreme, and was aggravated by breathing and by local pressure. It was relieved by an injection of hydrocortisone. The periosteal chest wall structures apparently were involved. This symptom may be added to the triad of pneumonitis, pleurisy and pericarditis found in the post-myocardial syndrome. The periosteal involvement either causes chest pain, or contributes to chest pain caused by pleural or pericardial involvement, or both. Its presence can be diagnosed by physical examination. The response to cortisone indicates an allergic-inflammatory etiology. The fact that eosinophilia was present during the painful episode in one patient also indicates an allergic factor in its origin.

CORONARY THROMBOSIS, CEREBRAL VASCULAR ACCIDENT AND PULMONARY EMBOLISM IN LEPROSY.

Rogers, J. H. *Ann. Int. Med.* **53:** 746 (Oct.) 1960.

The incidence of coronary thrombosis among 101 deaths in persons with leprosy was 9 per cent compared with 29 per cent among a control group (physicians with cause of death listed in the obituaries of the *J.A.M.A.*). The incidence of cardiovascular accident in the two groups was 5 and 17 per cent, and of malignant disease 20 and 9 per cent, respectively. This study is a sequel to a study on tuberculosis; a similar postulate is presented that leprosy, like tuberculosis, provokes a response in the body that has a protective action against these diseases. This may be associated with an *in vivo* hypocoagulable state of the blood mediated through an increase in the concentration of plasma globulins. It is believed that this may be brought about by formation of a complex of the unusual globulins with clotting factors, or by increased fibrinolytic activity, or both. Should these concepts prove to be correct, the author thinks that basic information necessary for the development of immunization against thrombosis will have been provided.

VERTEBRAL ARTERY COMPRESSION IN CERVICAL SPONDLYOSIS. ARTERIOGRAPHIC DEMONSTRATION DURING LIFE OF VERTEBRAL ARTERY INSUFFICIENCY DUE TO ROTATION AND EXTENSION OF THE NECK.

Sheehan, S.; Bauer, R. B., and Meyer, J. S. *Neurology* **10:** 968 (Nov.) 1960.

In 26 cases a diagnosis of "spondylotic vertebral artery compression" was confirmed by arteriography. This syndrome is characterized by symptoms of vertebral-basilar artery insufficiency. It can be diagnosed clinically with subsequent confirmation by angiography. A percutaneous technic is described in which the vertebral artery is injected with contrast medium after catheterization of the brachial artery under local anesthesia. The disease occurs most commonly in the sixth decade. The fact that it is more common among males may be related to the more frequent occurrence in them of occupational injury to the neck. The symptoms include dizziness, blurred vision, headache, and ataxia. The "drop attack" in which the patient collapses without losing consciousness is a pathognomonic sign. Signs due to vertebral artery compression are bilateral or unilateral spasticity, cerebellar signs, nystagmus, visual field disturbances, gaze palsy, internuclear ophthalmoplegia, fifth, seventh, eighth, ninth, tenth and twelfth nerve weakness, and hemisensory loss. Signs due to nerve-root compression—wasting of upper extremities, fasciculation, loss of tendon jerks, segmental sensory loss in the upper extremities and trunk—may or may not be present. Atherosclerosis or arteriosclerosis of the cerebral vessels is common, and predisposes to development of symptoms. Rotation or hyperextension of the neck will produce symptoms

comparable to those of which the patient complains. Results of the carotid compression test are negative except when the neck is rotated or extended. Electroencephalographic slowing appears only when the head is rotated with the carotid artery compressed. This is being investigated as a diagnostic test. Roentgenograms of the cervical spine will show spondylosis. Carotid arteriograms will show the presence of arteriosclerosis or atherosclerosis. The vertebral arteriograms will show marked displacement and/or compression by osteophytes, more marked upon rotation of the head. Treatment consists of bed rest for three weeks and avoidance of hyperextension and rotation of the head with, at times, a neck collar to prevent excessive movement of the neck. In patients with severe ischemia of the brain stem or occipital lobes, anticoagulant therapy is used in the belief that, because of severe compression and stenosis of the vertebral artery there may be deposits of mural thrombus, with possible embolization. Anticoagulant therapy has been successful, but it is also thought that the disease may have a more benign course than vertebral-basilar atherosclerosis, that recovery from attacks may be more prompt, and that a fatal outcome and severe disability may be less common. A surgical approach, with fixation of the neck to limit motion and decompression of the transverse foramina, may be feasible in some patients. These procedures carry the risk of trauma to the diseased vessel with resultant thrombosis, and of trauma to the cervical nerve.

USE OF A LONG-ACTING QUINIDINE PREPARATION IN THE REVERSION OF ATRIAL FIBRILLATION.

Stewart, J. T. *Am. J. Cardiol.* **6:** 961 (Nov.) 1960.

A long-acting quinidine preparation, Quinaglute Dura-Tabs S.M., was administered to 18 patients with atrial fibrillation. Of 15 patients between the ages of 57 and 77, one had luetic aortic insufficiency and the others arteriosclerotic heart disease. Four also had hypertension. The 3 remaining patients in the series had valvular lesions of rheumatic heart disease. Thirteen patients of the entire group had congestive heart failure. The duration of fibrillation was from two weeks to eight years. Each patient was digitalized before reversion of fibrillation was attempted. Initially, 0.6 Gm. of quinidine gluconate was given every eight hours for three days. If no reversion to sinus rhythm occurred, and there was no evidence of toxicity, the dose was increased to 0.9 Gm. every eight hours. Conversion to normal sinus rhythm occurred by the third day in 7 patients, by the fourth to sixth day in 7, by the eighth day in 1, and by the twentieth day in 1 who had a staphylococcal abscess. Therapy failed in 1 patient with rheumatic aortic valvular disease in whom ventricular tachycardia developed on the eighth day of therapy. The dosage schedule in 1 patient commenced with quinidine sulfate; when atrial fibrillation persisted, medication was changed to 0.6 Gm. of quinidine gluconate twice daily, and sinus rhythm was restored. In addition to the ventricular tachycardia (1 case) other side-effects were moderate gastro-intestinal symptoms in one patient and tinnitus in another. These disappeared upon reduction of the dosage to a maintenance level.

STUDIES ON GASTRIC SECRETORY FUNCTION IN THE AGED (JAPANESE TEXT).

Tanaka, T. *Sapporo med. J.* **14:** (1–2): 59, 1958; through Excerpta med (Gerontol. & Geriatrics) **3:** 129 (March) 1960.

A study of gastric secretory function in the aged, with special reference to the secretion of high-molecular components of the gastric juice, was carried out. Samples of gastric juice were drawn after insulin stimulation from 77 persons past the age of 60 years who had no signs or symptoms of gastro-enterologic disease. These were compared with samples obtained from healthy non-senescent adults and from patients with gastric carcinoma. Gastric juice samples were analyzed for acidity (Töpfer method), pepsin activity (Grützner method), total nitrogen (micro-Kjeldahl method), total dissolved mucin, dissolved mucoprotein (Mp) and mucoproteose (Mps) (tyrosine method after fractionation by the method

of Glass), polarographic protein wave (filtrate method), and hexosamine (Elson-Morgan method). Values were compared with values for histamine-stimulated gastric juice samples obtained from the same subjects. Blood sugar and blood pressure curves after intravenous insulin were determined in each case. The secretory function of the stomach was remarkably reduced in senescent people, the degree of reduction being to some extent proportionate to age. This finding applies not only to the yields and to HCl contents but also to the protein fractions—Mp in particular. The Mps showed an increase, rather than a decrease, in spite of a marked reduction in Mp content. Most cases studied by insulin stimulation showed a temporary decrease in polarographic activity, a phenomenon previously designated as "polarographic carcinoma curve." Hyperacidity and/or higher pepsin activity, in comparison to the acidity of the samples, were often observed. The decrease of the blood sugar level in response to injection of insulin was relatively slower than in normal adults, with consequent delayed secretion curves for HCl and Mp.

AN INVESTIGATION OF THE FAMILIAL ASPECTS OF CARCINOMA OF THE PROSTATE.
Woolf, C. M. *Cancer* **13:** 739 (July–Aug.) 1960.

A study of the parents and brothers and sisters of 228 males who died of carcinoma of the prostate at a mean age of 74 years supports the hypothesis that prostatic carcinoma has a genetic component that is organ specific. Two hundred and twenty-eight families were analyzed. Data on causes of death for the male relatives, and for controls matched as closely as possible, were analyzed by the double dichotomy method of sequential analysis. Deaths from cancer of the prostate were three times more frequent in the male relatives than in the controls. The number of deaths from cancer in the mothers and sisters was approximately the same as among the controls. The number of other types of cancer which caused death in the male and female relatives was numerically greater but not significantly increased over the number observed in the controls. All of these results favor the familial tendency hypothesis.

THE USE OF ANTICOAGULANTS IN CORONARY HEART DISEASE. PROGRESS AND PROBLEMS: 1960
Wright, I. S. *Circulation* **22:** 608 (Oct.) 1960.

The use of anticoagulant therapy in the treatment of acute myocardial infarction is generally accepted. It should be used in most cases, except when a contraindication or lack of facilities exists. Heparin may be used in the initial stages of anticoagulant therapy, especially when there is need for rapid action. The evidence now strongly favors long-term anticoagulant therapy after one or more myocardial infarctions in men. The evidence for its use in women is less conclusive, but the available figures are too few for final evaluation. The provision of adequate long-term anticoagulant care for those whose condition justifies its use is becoming a major social, economic and technical problem. This is a challenge for the medical profession, the clinical pathology societies, the medical schools, and the public health services. Evidence is accumulating that anticoagulant therapy favorably affects the incidence of morbidity and death in patients who suffer from angina pectoris due to coronary artery disease. Further studies are needed in this area. It is possible to perform safely minor and even some major operations while patients are maintained with anticoagulant therapy. This reduces the risk of thrombo-embolic complications. Patients receiving anticoagulant therapy should be given instruction regarding the effects of salicylates, antibiotics, other drugs, excessive alcohol, and various illnesses on the prothrombin activity. The Quick one-stage test carefully performed is satisfactory for most cases. However, many patients are sensitive, resistant, or otherwise difficult to control with anticoagulant therapy, and for these more sensitive tests are indicated. It is advantageous for hospitals to set up anticoagulant services in order to make available special knowledge regarding the problems that arise from this type of treatment and to help in obtaining maximal benefit from it. An

operating plan is presented as it functions at the New York Hospital. (From author's conclusions.)

IL TEMPO DI CIRCOLO POLMONARE ED ALTRE MISURE CARDIODINAMICHE NEL VECCHIO QUALI RISULTANO DAL RADIOCARDIOGRAMMA (LUNG CIRCUIT TIME AND OTHER CARDIODYNAMIC MEASUREMENTS IN THE ELDERLY DETERMINED RADIOCARDIOGRAPHICALLY).

Zurlo, A.; Grandonico, F., and Gallini, R. *G. Gerontol.* **7** (4): 353, 1959; through Excerpta med. (Gerontol. & Geriatrics) **3:** 129 (March) 1960.

A radiocardiographic investigation was made in 15 normal aging subjects (60–72 years of age), and cardiac output was found to be less than in younger people (average value, 4,787 ml. per minute versus 5,881 ml. per minute). This diminution was considered to be a consequence of the different heart rate, as the stroke output was practically the same in the two groups. The pulmonary mean time (peak-to-peak time) was found to be longer in elderly subjects (average value, 6.24 seconds versus 4.37 seconds). Also the "central blood volume" was found to be greater in the elderly group (531 ml. versus 392 ml.). The right ventricular output rate was the same in the two groups (average value, 36 per cent). Right telediastolic and diastolic residual volume showed little difference—179 and 116 ml. in elderly subjects versus 168 and 105 ml. in the younger ones.

NEWS AND NOTICES

NEW COOK BOOK DESIGNED TO PREVENT OVERWEIGHT THROUGH EATING HABITS

For the first time, a cook book has been prepared which is specifically designed to help prevent overweight through the development of better eating habits. It is Wesson's new "Cook Book of Glorious Eating for Weight Watchers," a 100-page volume that fills the long-felt need for a weight control plan that is workable for everybody in the family.

The Cook Book is now being made available to physicians, free of charge, prior to its release date for the general public. Forms will also be provided physicians to enable their patients to receive a free copy of the cook book. Requests should be set to Wesson, Box 777, Hinsdale, Illinois.

Featuring recipes and menus that provide satiety and appetite appeal, the full-color cook book presents realistic regimens that are built around good, natural, readily-available foods enhanced by delicious methods of preparation. In place of "fad diets," or tastless abstinence, it provides for appetizing meals which are expected to help Americans develop the healthful eating habits that can prevent overweight . . . the nation's #1 health problem.

Complete daily menus are offered at 3 calorie levels . . . 1200, 1800, and 2600. Calorie levels are related to "best" weight by sex, age, size and extent of activity, and a weight chart and method of determining the individual's weight maintenance calorie requirements are included.

The menus fulfill the recommended dietary allowances of the Food and Nutrition Board of the National Research Council. Each menu provides the proper amount of protein, carbohydrates, fat and other essential nutrients.

In addition to the menus and 248 calorie-counted recipes, the new "weight watchers" cook book offers vital principles of good nutrition. These are included to help the homemaker plan her own properly balanced, calorie-controlled menus. For example, the book shows how, with simple subtractions or additions to the same basic menu, each family member can be served delicious, satisfying menus according to his individual calorie requirements.

PROGRAM

EIGHTEENTH ANNUAL MEETING

OF THE

AMERICAN GERIATRICS SOCIETY

Thursday, June 22 and Friday, June 23, 1961

Waldorf-Astoria Hotel, New York City

THURSDAY Morning, June 22, 1961

SERT ROOM

8:00 Registration

9:00 Presiding Officer: Dr. Edward L. Bortz

Energy Supply and Maintenance—Panel Discussion

Dr. Laurance W. Kinsell, Moderator; Director, Institute for Metabolic Research, Highland-Alameda County Hospital, Oakland, California.

Dr. Nathan W. Shock, Chief, Gerontology Branch; National Heart Institute and the Baltimore City Hospitals, Baltimore, Maryland.

Dr. Edgar S. Gordon, Professor of Medicine, University of Wisconsin School of Medicine, Madison, Wisconsin.

Dr. Daniel Rudman, Asst. Professor of Medicine, Columbia University College of Physicians & Surgeons, New York, N. Y.

10:30 Intermission

11:00 Presiding Officer: Dr. Edward Henderson

The Interrelation of Carbohydrate and Lipid Metabolism—Panel Discussion

Fatty Acid Synthesis in Cell-Free Systems

Dr. Samuel Abraham, Assoc. Research Physiologist, Dept. of Physiology, University of California, Berkeley, Calif.

Adipose Tissue as a Site of Hormonal and Nutritional Regulation

Dr. Albert E. Renold, Asst. Professor of Medicine, Harvard University Medical School, Boston, Mass.

Factors Affecting Cholesterol Biosynthesis and Degradation

Dr. David Kritchevsky, Assoc. Member, Wistar Inst. of Anatomy & Biology, Philadelphia, Pa.; Asst. Professor of Biochemistry, Univ. of Pennsylvania School of Medicine.

12:30 Luncheon

THURSDAY Afternoon, June 22, 1961

SERT ROOM

1:45 Presiding Officer: Dr. Warren H. Cole

Endocrine Regulatory Mechanisms as People Age—Panel Discussion

Moderator, Dr. Thomas H. McGavack, Chief, Intermediate Service, Veterans Administration Center, Martinsburg, West Virginia, and Professional Lecturur in Medicine, George Washington Univ. School of Medicine, Washington, D. C.

Neuroendocrine Relationships

Dr. Russell M. Wilder, Jr., Instructor in Internal Medicine, University of Kansas, Topeka, Kansas.

The Pituitary

Dr. Raymond V. Randall, Consultant in Medicine, Mayo Clinic, Rochester, Minn.

The Thyroid

Dr. James A. Pittman, Jr., Chief, Radioisotope Service, Veterans Admin. Hospital Birmingham, Alabama.

The Adrenals

Dr. Roger B. Hickler, Chief, Geriatric Unit, Peter Bent Brigham Hospital, Boston, Mass.

The Gonads

Dr. Reginald A. Shipley, Associate Professor of Medicine, Western Reserve University, Cleveland, Ohio.

Intermission

3:30 Presiding Officer: Dr. Frank Glenn

Fatigue—Panel Discussion

Moderator, Dr. David B. Dill, Medical Research Directorate, U. S. Army Chemical Research Laboratories, Maryland.

Dr. Steven M. Horvath, Division of Research, Lankenau Hospital, Philadelphia, Penna.

Dr. Lucien Brouha, Physiologist, Haskell Laboratory, E. I. DuPont Co., Wilmington, Del.

4:45 BUSINESS MEETING

6:30 ANNUAL RECEPTION AND DINNER
Louis XVI Suite, Dress Optional
Presentation of the Willard O. Thompson Memorial Award
Music

FRIDAY Morning, June 23, 1961

SERT ROOM

8:00 REGISTRATION

9:00 Presiding Officer: Dr. Edward B. Allen
FROM RETIREMENT TO THE SECOND CAREER—PANEL DISCUSSION

Mr. Dwight S. Sargent, Personnel Director, Consolidated Edison Co. of New York, N. Y.

Mr. Charles E. Odell, Director, Older & Retired Workers, United Auto Workers AFL-CIO, Detroit, Michigan.

Mr. Matthew Radom, Assoc. Professor of Management, Rutgers University, New Brunswick, New Jersey.

Mr. Harold Schroeder, Asst. Vice President, American Telephone & Telegraph Co., New York, N. Y.

10:30 INTERMISSION

11:00 Presiding Officer: Dr. William Hammond
MAINTENANCE OF A HEALTHY LOCOMOTOR SYSTEM IN OLDER INDIVIDUALS—PANEL DISCUSSION

Moderator, Dr. William B. Rawls, Attending Physician and Chief of Arthritis Clinic, New York Polyclinic Medical School & Hospital, New York, N. Y.

Dr. L. Maxwell Lockie, Professor of Therapeutics, University of Buffalo, School of Medicine, Buffalo, N. Y.

Dr. Richard H. Freyberg, Professor of Clinical Medicine, Cornell University Medical College, New York, N. Y.

Dr. Charles H. Slocumb, University of Minnesota Graduate School, Minneapolis-Rochester, Minn. (Professor of Medicine) .

Dr. James A. Coss, Jr., Assistant in Medicine, Columbia Presbyterian Medical Center, New York, N. Y.

12:30 LUNCHEON

FRIDAY Afternoon, June 23, 1961

SERT ROOM

1:45 Presiding Officer: Dr. A. Clayton McCarty
SURVIVAL—PANEL DISCUSSION
SURVIVAL POTENTIAL OF OLDER INDIVIDUALS RELATIVE TO THEIR PHYSICAL AND MENTAL RESOURCES

Dr. J. Murray Steele, Director, New York University Research Service, Goldwater Memorial Hospital, New York, N. Y.
ROLE OF THE OLDER INDIVIDUALS IN NATIONAL DEFENSE

Dr. Cecil H. Coggins, Rear Admiral (MC) USN (Ret.)
ROLE OF OLDER INDIVIDUALS TO SUSTAIN NATIONAL ECONOMY AND PROMOTE WELFARE

Dr. Albert R. Behnke, Naval Radiological Division, San Francisco, California.
INTERMISSION

3:30 Presiding Officer: Dr. E. David Sherman
MOTIVATION AND MORALE IN OLDER INDIVIDUALS
MOTIVATION
Dr. Jack Weinberg, Asst. Professor of Psychiatry, University of Illinois, Chicago, Illinois
MORALE
Dr. Mathew Ross, Medical Director, American Psychiatric Assoc., Washington, D. C.; Consultant, Office of the Surgeon-General, U. S. Army
4:30 FILM "EXTERNAL CARDIAC MASSAGE" (a 22-minute color-and-sound film)
Presented by the American Geriatrics Society in cooperation with Smith Kline & French Laboratories.

SATURDAY Morning, June 24, 1961

ASTOR GALLERY

Presentation for Lay Section

8:30 REGISTRATION
9:30 Moderator: Dr. Hollis E. Clow, Psychiatrist, Westchester Division, New York Hospital
THE INTEREST OF THE JUNIOR LEAGUES IN AGING PEOPLE
Mrs. Alexander S. Parr, Executive Staff Administrator, Junior Leagues of America, New York, N. Y.
10:00 A PATTERN FOR ACTION IN GERIATRICS
Mrs. Harold V. Milligan, Chairman of Division on Gerontology, General Federation of Women's Clubs, New York, N. Y. (A Federation Resource Group will be present.)
10:30 A SENIOR PERSONNEL EMPLOYMENT COMMITTEE: A VOLUNTEER SERVICE AND HOW IT WORKS
Mr. Edwin J. Hiller, Director, Senior Personnel Employment Services, White Plains, N. Y. (Original volunteer organization in this field.)
11:00 Address by: Dr. Edward L. Bortz, President, American Geriatrics Society, Past-President, American Medical Association.
11:15 INTERMISSION—Coffee
11:30 URGENT DEVELOPMENT OF THE PHILOSOPHY OF LEISURE TIME IN AN AGING POPULATION
Dr. Alexander Reid Martin, Psychiatrist, Psychoanalyst, Lecturer, Chairman American American Psychiatric Association Standing Committee on Leisure Time and Its Uses.
12:00 ORGANIZATIONAL MEETING AND ELECTION OF LAY SECTION OFFICERS
12:30 ADJOURNMENT

BOARD & COMMITTEE MEETINGS

Tuesday, June 20, 1961
9:30 AM Constitution & Bylaws Committee and Board of Directors
4:30 PM Finance Committee
Wednesday, June 21, 1961
9:30 AM Committee Meetings: Legislative
Education & Research
Constitution & Bylaws (continued)
11:00 AM National Advisory Committee to Industry
Publications and V.I.P.
2:00 PM Committee for Activation of Lay Group
Exhibits
Insurance
Public Relations
Membership

3:00 PM Advisory Council
7:00 PM Board of Directors

Thursday, June 22, 1961

8:00 AM Board of Directors

Friday, June 23, 1961

5:15 PM Board of Directors, Advisory Council, Chairmen and Members of Committees Liaison and Planning Meeting

Saturday, June 24, 1961

12:30 PM Board of Directors and Advisory Council